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I, JULIE BILLINGSLEY, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2003904068 for a patent by FUJISAWA PHARMACEUTICAL CO., LTD. as filed on 01 August 2003.

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JULIE BILLINGSLEY  
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Fujisawa Pharmaceutical Co., Ltd.

**A U S T R A L I A**

**Patents Act 1990**

**PROVISIONAL SPECIFICATION**

for the invention entitled:

**"Inhibitor of Cox"**

The invention is described in the following statement:

D E S C R I P T I O N

INHIBITOR OF COX

5       TECHNICAL FIELD

This invention relates to imidazole compounds and pharmaceutically acceptable salts thereof having pharmacological activity.

Moreover, this invention relates to medicament or pharmaceutical composition comprising the above mentioned imidazole compounds or pharmaceutically acceptable salts thereof as an active ingredient.

10

BACKGROUND ART

Some imidazole derivatives having anti-inflammatory and/or analgesic activities have been known, for example, WO 96/03388. However, all of compounds disclosed in this document are substituted by sulfonyl group on imidazole ring. And the compounds disclosed in WO 96/03388 selectively inhibit cyclooxygenase-II (COX-II) over cyclooxygenase-I (COX-I).

20      DISCLOSURE OF THE INVENTION

As a result of studies on the synthesis of imidazole compounds and their pharmacological activity, the inventors of this invention have found that the imidazole compounds of this invention have superior activity of inhibiting COX (especially, COX-I inhibiting activity).

25      So, this invention relates to imidazole compounds, which have pharmaceutical activity such as COX inhibiting activity, to a medicament and a pharmaceutical composition containing the imidazole compounds.

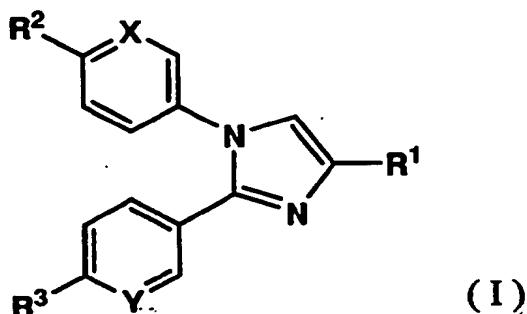
Accordingly, one object of this invention is to provide the imidazole compounds, which have a COX inhibiting activity.

30      Another object of this invention is to provide a method for treatment and/or prevention and the imidazole compounds for use in the treatment and/or prevention of the disease associated with COX.

A further object of this invention is to provide a use of the imidazole compounds for manufacturing a medicament for treating or preventing the diseases and the analgesic agent comprising the imidazole compounds which is usable for treating and/or preventing pains.

5

The imidazole compounds of this invention can be represented by the following general formula (I):



10

[wherein

R¹ is (lower)alkyl, halogen-substituted (lower)alkyl,  
hydroxy-substituted (lower)alkyl, cycloalkyl, carbamoyl,  
N-[(lower)alkyl]carbamoyl, N,N-di[(lower)alkyl]carbamoyl,  
formyl, (lower)alkanoyl, carboxy, [(lower)alkoxy]carbonyl,  
cyano, cycloalkylcarbonyl or heterocycliccarbonyl;

15

R² is halogen, cyano, hydroxy, (lower)alkoxy,  
aryl[(lower)alkyl]oxy, [(lower)alkoxy]carbonyl,  
carbamoyl, formyloxy, (lower)alkanoyloxy,

20

[(lower)alkyl]sulfonyloxy, [halogen-substituted  
(lower)alkyl]sulfonyloxy or carboxy;

R³ is (lower)alkoxy, hydroxy, amino, [(lower)alkyl]amino, or  
di[(lower)alkyl]amino;

X and Y are each CH or N]

25

or pharmaceutically acceptable salts thereof.

In the above and subsequent description of the present specification,

suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

5 So, the "(lower)alkyl" means a straight or branched chain aliphatic hydrocarbon, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, or the like, and it is preferably (C<sub>1</sub>-C<sub>4</sub>)alkyl, more preferably (C<sub>1</sub>-C<sub>2</sub>)alkyl, most preferably methyl.

10 The "halogen" may include a fluorine atom, a chlorine atom, a bromine atom and an iodine atom, and is preferably a fluorine atom or a chlorine atom, more preferably a fluorine atom.

15 The "halogen-substituted (lower)alkyl" means a monovalent group in which the above lower alkyl is substituted by the above halogen atom(s), such as fluoromethyl, chloromethyl, difluoromethyl, dichloromethyl, dibromomethyl, trifluoromethyl, trichloromethyl, fluoroethyl, chloroethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl, 2,2,3,3-pentafluoroethyl, fluoropropyl, fluorobutyl, fluorohexyl, or the like, and it is preferably halogen-substituted (C<sub>1</sub>-C<sub>4</sub>)alkyl, more preferably halogen-substituted (C<sub>1</sub>-C<sub>2</sub>)alkyl, more preferably 20 fluorine-substituted (C<sub>1</sub>-C<sub>2</sub>)alkyl, more preferably fluorine-substituted methyl, most preferably difluoromethyl or trifluoromethyl.

25 The "hydroxy-substituted (lower)alkyl" means a monovalent group in which the above (lower)alkyl is substituted by a OH group, such as hydroxymethyl, hydroxyethyl, hydroxypropyl, 1-hydroxyisopropyl, 2-hydroxyisopropyl, hydroxybutyl, hydroxyisobutyl, hydroxy-tert-butyl, hydroxyhexyl, or the like, and it is preferably hydroxy-substituted (C<sub>1</sub>-C<sub>4</sub>)alkyl, more preferably hydroxy-substituted (C<sub>1</sub>-C<sub>2</sub>)alkyl, most preferably hydroxymethyl.

30 The "cycloalkyl" means (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl group, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, adamantyl, or the like, and it is preferably

(C3-C6)cycloalkyl, more preferably (C3-C5)cycloalkyl, most preferably cyclopropyl.

The "N-[(lower)alkyl]carbamoyl" means a carbamoyl group substituted by the above (lower)alkyl group on nitrogen atom, such as methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, isobutylcarbamoyl, tert-butylcarbamoyl, pentylcarbamoyl, hexylcarbamoyl, or the like, and it is preferably N-[(C1-C4)alkyl]carbamoyl, more preferably N-[(C1-C2)alkyl]carbamoyl.

10 The "N,N-di[(lower)alkyl]carbamoyl" means a carbamoyl group substituted by the same or different above two (lower)alkyl groups on nitrogen atom, such as dimethylcarbamoyl, diethylcarbamoyl, dipropylcarbamoyl, diisopropylcarbamoyl, dibutylcarbamoyl, diisobutylcarbamoyl, dipentylcarbamoyl, dihexylcarbamoyl, 15 ethylmethylcarbamoyl, methylpropylcarbamoyl, butylmethylcarbamoyl, ethylpropylcarbamoyl, butylethylcarbamoyl, or the like, and it is preferably di[(C1-C4)alkyl]carbamoyl, more preferably di[(C1-C2)alkyl]carbamoyl.

20 The "(lower)alkanoyl" means carbonyl group which is substituted by the above (lower)alkyl groups, such as acetyl, propionyl (ethylcarbonyl), butyryl, isobutyryl (isopropylcarbonyl), pivaloyl, valeryl, isovaleryl, hexanoyl, and the like, and it is preferably (C2-C5)alkanoyl, more preferably (C2-C4)alkanoyl.

25 So, "(lower)alkanoyloxy" may be exemplified by acetyloxy, propionyloxy (ethylcarbonyloxy), butyryloxy, isobutyryloxy (isopropylcarbonyloxy), pivaloyloxy, valeryoxyl, isovaleryloxy, hexanoyloxy, and the like, and it is preferably (C2-C5)alkanoyloxy, more preferably (C2-C4)alkanoyloxy.

30 The "(lower)alkoxy" means a straight or branched chain aliphatic hydrocarbon oxy group, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentoxy, hexoxy, or the like, and it is preferably (C1-C4)alkoxy, more preferably (C1-C2)alkoxy, most

preferably methoxy.

The "cycloalkylcarbonyl" means carbonyl group substituted by the above cycloalkyl group, such as cyclopropylcarbonyl,

cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl,

5 cycloheptylcarbonyl, norbornylcarbonyl, adamantylcarbonyl, or the like, and it is preferably [(C<sub>3</sub>-C<sub>6</sub>)cycloalkyl]carbonyl, more preferably [(C<sub>3</sub>-C<sub>5</sub>)cycloalkyl]carbonyl.

The "heterocycle" means 5- or 6-membered saturated heterocyclic group which contains at least one hetero atom such as nitrogen, oxygen,

10 sulfur atom. The "heterocycle" may include 5-membered heterocyclic group such as pyrrolidinyl, imidazolidinyl, pyrazolidinyl,

tetrahydrothiophenyl, tetrahydrofuranyl, oxazolidinyl,

isoxazolidinyl, thiazolidinyl, isothiazolidinyl, or the like; and 6-membered heterocyclic group such as piperidinyl, piperazinyl,

15 morpholinyl, thiomorpholinyl, or the like.

So, the "heterocycliccarbonyl" may be exemplified pyrrolidinylcarbonyl, imidazolidinylcarbonyl, pyrazolidinylcarbonyl,

tetrahydrothiophenylcarbonyl, tetrahydrofuranylcarbonyl,

oxazolidinylcarbonyl, isoxazolidinylcarbonyl, thiazolidinylcarbonyl

20 as 5-membered heterocycliccarbonyl group; and piperidinylcarbonyl, piperazinylcarbonyl, morpholinylcarbonyl, thiomorpholinylcarbonyl as 6-membered heterocycliccarbonyl group. And it is preferably

(heterocyclic containing nitrogen atom)carbonyl or 6-membered heterocycliccarbonyl, more preferably piperidinylcarbonyl.

25 The "aryl[(lower)alkyl]oxy," means the above mentioned (lower)alkoxy group which is substituted with aryl group, such as

benzyloxy, nephtylmethoxy, indenylmethoxy, phenetyl, nephtylethyl,

phenylpropyl, phenylbutyl, phenylhexyl, or the like, and it is.

30 preferably aryl[(C<sub>1</sub>-C<sub>2</sub>)alkyl]oxy, more preferably arylmethoxy, most preferably benzyloxy.

The "[(lower)alkoxy]carbonyl" means a -CO<sub>2</sub>-[(lower)alkyl] group, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl.

isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, pentoxy carbonyl, hexoxycarbonyl, and the like, and it is preferably [(C<sub>1</sub>-C<sub>4</sub>)alkoxy]carbonyl, more preferably ethoxycarbonyl.

5       The "[lower)alkyl]sulfonyl" means a sulfonyl group substituted with (lower)alkyl group mentioned above, such as methanesulfonyl, ethanesulfonyl, isopropanesulfonyl, tert-butanesulfonyl, and the like, and it is preferably (C<sub>1</sub>-C<sub>4</sub>)alkanesulfonyl, more preferably (C<sub>1</sub>-C<sub>2</sub>)alkanesulfonyl, most preferably methanesulfonyl.

10      So, "[lower)alkyl]sulfonyloxy" may be exemplified by methanesulfonyloxy, ethanesulfonyloxy, isopropanesulfonyloxy, tert-butanesulfonyloxy, and the like, and it is preferably (C<sub>1</sub>-C<sub>4</sub>)alkanesulfonyloxy, more preferably (C<sub>1</sub>-C<sub>2</sub>)alkanesulfonyloxy, most preferably methanesulfonyloxy.

15      The "[halogen-substituted (lower)alkyl]sulfonyl" means a sulfonyl group substituted with halogen-substituted (lower)alkyl mentioned above, such as trifluoromethanesulfonyl, and the like, and it is preferably halogen-substituted (C<sub>1</sub>-C<sub>4</sub>)alkylsulfonyl, more preferably halogen-substituted (C<sub>1</sub>-C<sub>2</sub>)alkylsulfonyl, most preferably trifluoromethanesulfonyl.

20      So, "[halogen-substituted (lower)alkyl]sulfonyloxy" may be exemplified by trifluoromethanesulfonyloxy, and the like, and it is preferably halogen-substituted (C<sub>1</sub>-C<sub>4</sub>)alkanesulfonyloxy, more preferably halogen-substituted (C<sub>1</sub>-C<sub>2</sub>)alkanesulfonyloxy, most preferably trifluoromethanesulfonyloxy.

25      The "[lower)alkyl]amino" means a amino group substituted by the above lower alkyl group, such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, tert-butylamino, pentylamino, hexylamino, or the like, and it is preferably [(C<sub>1</sub>-C<sub>4</sub>)alkyl]amino, more preferably [(C<sub>1</sub>-C<sub>2</sub>)alkyl]amino.

30      The "di[(lower)alkyl]amino" means a amino group substituted by the same or different above (lower)alkyl groups, such as dimethylamino,

diethylamino, dipropylamino, diisopropylamino, dibutylamino,  
diisobutylamino, dipentylamino, dihexylamino, ethylmethylamino,  
methylpropylamino, butylmethylamino, ethylpropylamino,  
butylethylamino, or the like, and it is preferably di[(C<sub>1</sub>-C<sub>4</sub>)alkyl]amino,  
5 more preferably di[(C<sub>1</sub>-C<sub>2</sub>)alkyl]amino.

The combination of X and Y is X and Y are each CH, X is N and Y  
is CH, X is CH and Y is N, X and Y are each N, preferably X and Y are  
each CH, X is N and Y is CH, or X is CH and Y is N, and any of these  
three combination are preferable.

10

The compounds of formula (I) may contain one or more asymmetric  
centers and thus they can exist as enantiomers or diastereoisomers.  
This invention includes both mixtures and separate individual isomers.

15 The compounds of the formula (I) may also exist in tautomeric forms  
and the invention includes both mixtures and separate individual  
tautomers.

The compounds of the formula (I) and its salts can be in a form  
of a solvate, which is included within the scope of the present invention.  
The solvate preferably include a hydrate.

20 Also included in the scope of invention are radiolabelled  
derivatives of compounds of formula (I) which are suitable for biological  
studies.

The imidazole compounds of this invention can be converted to salt  
according to a conventional method. Suitable salts of the compounds  
25 (I) are pharmaceutically acceptable conventional non-toxic salts and  
include a metal salt such as an alkali metal salt (e.g., sodium salt,  
potassium salt, etc.) and an alkaline earth metal salt (e.g., calcium  
salt, magnesium salt, etc.), an ammonium salt, an organic base salt  
(e.g., trimethylamine salt, triethylamine salt, pyridine salt, picoline  
30 salt, dicyclohexylamine salt, etc.), an organic acid salt (e.g., acetate,  
maleate, tartrate, methanesulfonate, benzenesulfonate, formate,  
toluenesulfonate, trifluoroacetate, etc.), an inorganic acid salt (e.g.,

hydrochloride, hydrobromide, sulfate, phosphate, etc.), a salt with an amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.), or the like.

5       The imidazole compound (I) may preferably include  
wherein

R<sup>1</sup> is (lower)alkyl, halogen-substituted (lower)alkyl, cycloalkyl,

N,N-di[(lower)alkyl]carbamoyl, (lower)alkanoyl, or cyano;

R<sup>2</sup> is halogen, cyano, hydroxy, or lower alkoxy;

10      R<sup>3</sup> is lower alkoxy;

X and Y are each CH, X is N and Y is CH, or X is CH and Y is N.

And in the each definition of the compound formula(I), preferably,

(1) R<sup>1</sup> is (lower)alkyl, halogen-substituted (lower)alkyl, cycloalkyl, carbamoyl, N,N-di[(lower)alkyl]carbamoyl, (lower)alkanoyl or cyano.

(2) R<sup>1</sup> is (lower)alkyl, halogen-substituted (lower)alkyl, cycloalkyl,

(3) R<sup>1</sup> is (C1-C4)alkyl, halogen-substituted (C1-C4)alkyl or (C3-C6)cycloalkyl.

20      (4) R<sup>1</sup> is (C1-C2)alkyl, halogen-substituted (C1-C2)alkyl or (C3-C5)cycloalkyl,

(5) R<sup>1</sup> is carbamoyl or N,N-di[(C1-C4)alkyl]carbamoyl.

(6) R<sup>1</sup> is carbamoyl or N,N-di[(C1-C2)alkyl]carbamoyl,

(7) R<sup>1</sup> is (C2-C4)alkanoyl or cyano,

25      (8) R<sup>2</sup> is halogen, cyano, hydroxy, (lower)alkoxy, aryl[(lower)alkyl]oxy, [(lower)alkoxy]carbonyl, carbamoyl or [halogen-substituted (lower)alkyl]sulfonyloxy,

(9) R<sup>2</sup> is halogen, cyano, hydroxy, (C1-C4)alkoxy, arylmethoxy, [(C1-C4)alkoxy]carbonyl, carbamoyl or [halogen-substituted

30      (C1-C4)alkyl]sulfonyloxy,

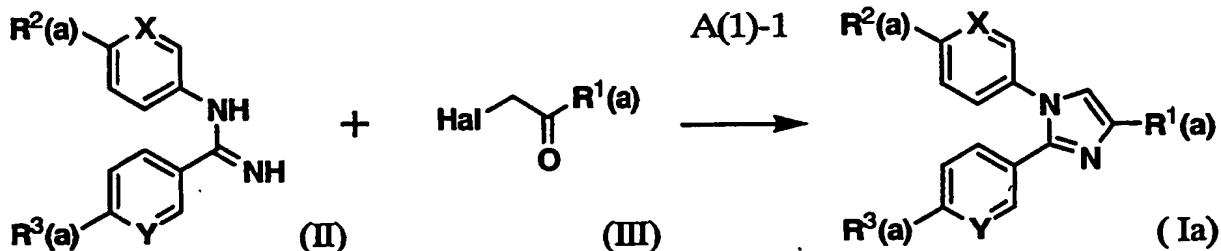
(10) R<sup>2</sup> is halogen, cyano, hydroxy or (C1-C2)alkoxy,

(11) R<sup>2</sup> is hydroxy or (C1-C2)alkoxy,

- (12) R<sup>3</sup> is (lower)alkoxy or hydroxy,  
 (13) R<sup>3</sup> is (C1-C4)alkoxy,  
 (14) R<sup>3</sup> is (C1-C2)alkoxy,  
 (15) X and Y are each CH,  
 5 (16) X is N and Y is CH,  
 (17) X is CH and Y is N.  
 (18) X and Y are each N.

10 The compound of the formula (I) of the present invention can be prepared according to the following process.

Process A(1)



15 In the above formulae, X and Y represent the same meanings as defined above. R<sup>1(a)</sup>, R<sup>2(a)</sup> and R<sup>3(a)</sup> represent the group in the definition of R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup>, respectively, which do not influence this process. Concretely, R<sup>1(a)</sup> represents (lower)alkyl, halogen-substituted (lower)alkyl, cycloalkyl, N,N-di[(lower)alkyl]carbamoyl, formyl, (lower)alkanoyl, [(lower)alkoxy]carbonyl, cyano or cycloalkylcarbonyl; R<sup>2(a)</sup> represents halogen, cyano, (lower)alkoxy, aryl[(lower)alkyl]oxy, [(lower)alkoxy]carbonyl, formyloxy, (lower)alkanoyloxy, [(lower)alkyl]sulfonyloxy or [halogen-substituted (lower)alkyl]sulfonyloxy; R<sup>3(a)</sup> represents is lower alkoxy. "Hal" represents halogen atom, especially, chlorine or bromine atom.

20 Process A(1) is the process for preparing the compound (Ia), which corresponds to compound (I) in which R<sup>1</sup> to R<sup>3</sup> are not reactive groups.

This process is carried out by reacting compound (II) and compound (III) in the presence of base to form imidazole ring.

Compound (II) may be purchased if it is commercial, or synthesized according to Processes B mentioned after or other general methods from commercial compounds. Compound (III) may be purchased if it is commercial, or synthesized according to general methods from commercial compounds, because compound (III) as starting compound for synthesis of compound (Ia) have comparatively simple structure.

The solvent employable in this process is not particularly limited so long as it is inactive in this reaction and may include alcohols such as methanol, ethanol, 2-propanol; ethers such as diisopropyl ether, tetrahydrofuran, dioxane; and mixed solvent of these.

The base employable in this process for making basic condition is not particularly limited so long as it accelerate this reaction and. may include alkali metal hydrogencarbonates such as lithium hydrogencarbonate, sodium hydrogencarbonate and potassium hydrogencarbonate; alkali metal carbonates such as lithium carbonate, sodium carbonate and potassium carbonate; alkaline earth metal carbonates such as magnesium carbonate and calcium carbonate; alkali metal hydroxides such as lithium hydroxide, sodium hydroxide and potassium hydroxide, preferably alkali metal hydrogencarbonates, especially sodium hydrogencarbonate.

The reaction temperature varies depending on the starting material, the solvent, etc., but it is usually from 50°C to 150°C, preferably from 60°C to 100°C or reflux condition.

The reaction time varies depending on the starting material, the solvent, the reaction temperature, etc., but it is usually from 1hr to 1day, preferably from 2hrs to 12hrs.

After the reaction, the reaction mixture is cooled to room temperature and evaporated in vacuo, then added water and extracted with organic solvent immiscible with water such as ethyl acetate. The organic layer is washed with water or the like, dried over anhydrous

magnesium sulfate or sodium sulfate, evaporated in vacuo, and the desired compound is purified by the conventional method such as silica gel column chromatography, recrystallization, etc.

According to the starting material, the heterocyclic ring is formed but not to form imidazole ring. In such case, the dehydration process is needed to form imidazole ring.

The dehydration process is carried out in the hot and acidic condition.

The solvent employable in this process is not particularly limited, but acid such as acetic acid, sulfuric acid or the like may be used as solvent.

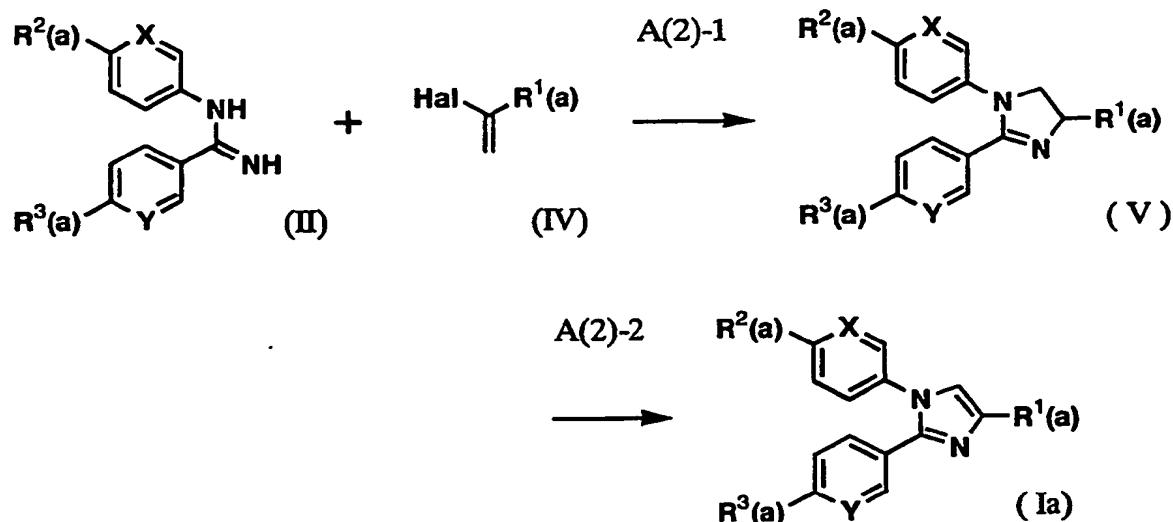
The reaction temperature varies depending on the starting material, the solvent, etc., but it is usually from 50°C to 200°C, preferably from 80°C to 150°C.

The reaction time varies depending on the starting material, the solvent, the reaction temperature, etc., but it is usually from 30min to 5hrs, preferably from 1hr to 3hrs.

After the reaction, the mixture is poured into basic water, and extracted with organic solvent insoluble with water such as ethyl acetate. The organic layer is washed with water or the like, dried over anhydrous magnesium sulfate or sodium sulfate, evaporated in vacuo, and the desired compound is purified by the conventional method such as silica gel column chromatography, recrystallization, etc.

Compound (Ia) can also be synthesized according to the following process.

### Process A(2)



5

In the above formulae,  $R^1(a)$ ,  $R^2(a)$ ,  $R^3(a)$ , X, Y and Hal represent the same meanings as defined above.

Process A(2) is the process for preparing the compound (Ia), which corresponds to compound (I) in which R<sup>1</sup> to R<sup>3</sup> are not reactive groups.

In this process, first, compound (II) is condensed to compound (IV) for synthesis of compound (V) (Process A(2)-1).

Process A(2)-1 is carried out under in the presence of Hunig's base (*N,N*-diisopropylethylamine).

15 Compound (IV) may be purchased if it is commercial, or synthesized according to general methods from commercial compounds, because compound (IV) have comparatively simple structure.

The solvent employable in this process is not particularly limited so long as it is inactive in this reaction and may include ethers such as diisopropyl ether, tetrahydrofuran, dioxane, preferably tetrahydrofuran.

The reaction temperature varies depending on the starting material, the solvent, etc., but it is usually from 50°C to 200°C, preferably

from 50°C to 120°C or reflux condition.

The reaction time varies depending on the starting material, the solvent, the reaction temperature, etc., but it is usually from 1hr to 2days, preferably 1hr to 5hrs or over night.

5 If the reaction does not proceed adequately, additional compound (IV) may be added.

After the reaction, the desired compound (V) is collected from the reaction mixture according to a conventional method. For example, after cooled to room temperature and evaporated in vacuo, the reaction 10 mixture is poured into water and extracted with organic solvent immiscible with water such as ethyl acetate. The organic solvent is washed with water or the like, dried over anhydrous magnesium sulfate or sodium sulfate, evaporated in vacuo, and the desired compound is purified by the conventional method such as silica gel column 15 chromatography, recrystallization, etc.

Process A(2)-2 is the oxidation process to form imidazole ring in the presence of catalyst.

The oxidative catalyst employable in this process is not particularly limited so long as it can catalyze the reaction from 20 4,5-dihydro-imidazole derivative (V) to imidazole derivative and may include manganese(IV) oxide ( $MnO_2$ ).

The solvent employable in this process is not particularly limited so long as it is inactive in this reaction and may include amides such as N,N-dimethylformamide, dimethylacetamide, hexamethylphosphoric 25 triamide; aromatic hydrocarbon such as benzene, toluene; or the like.

The reaction temperature varies depending on the starting material, the solvent, etc., but it is usually from 50°C to 200°C, preferably from 80°C to 120°C or reflux condition.

The reaction time varies depending on the starting material, the 30 solvent, the reaction temperature, etc., but it is usually from 1hr to 24hrs, preferably 2hrs to 12hrs.

If the reaction does not proceed adequately, additional catalyst

may be added.

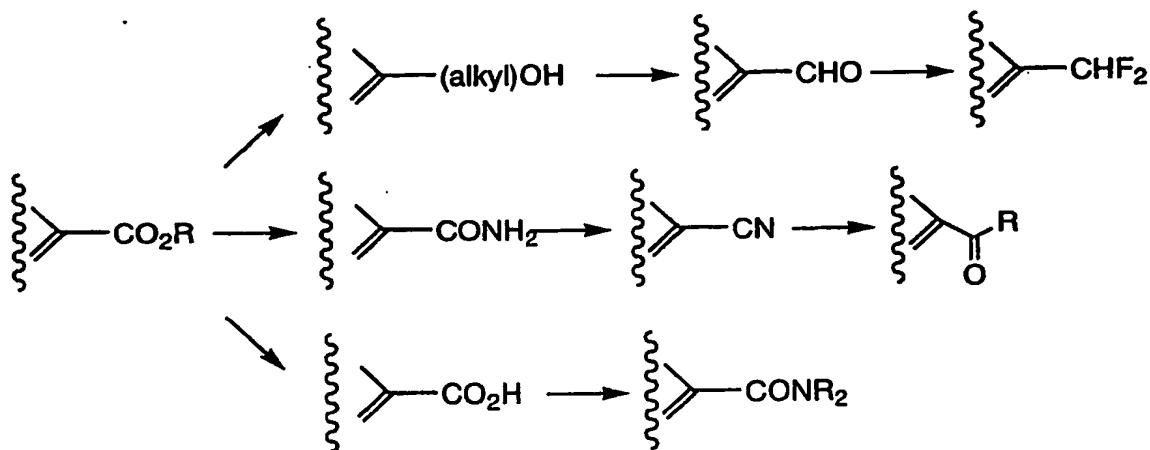
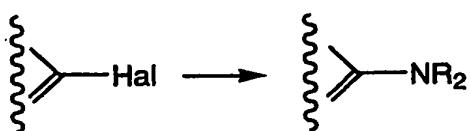
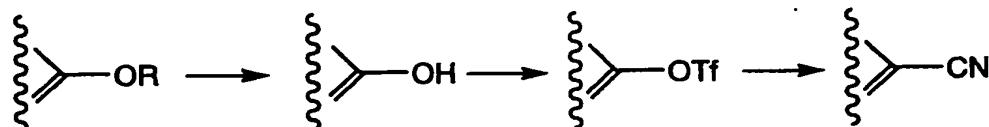
After the reaction, the mixture is cooled to room temperature and filtered to remove catalyst. The organic fraction is concentrated in vacuo, or poured into basic water, and extracted with organic solvent insoluble with water such as ethyl acetate. The organic layer is washed with water or the like, dried over anhydrous magnesium sulfate or sodium sulfate, evaporated in vacuo. The desired compound is purified by the conventional method such as silica gel column chromatography, recrystallization, etc.

10

Compound (Ia) can be transformed into compound (I) by functional group transformation, which is obvious to the person skilled in the organic chemistry. For example, such reactions are illustrated as following.

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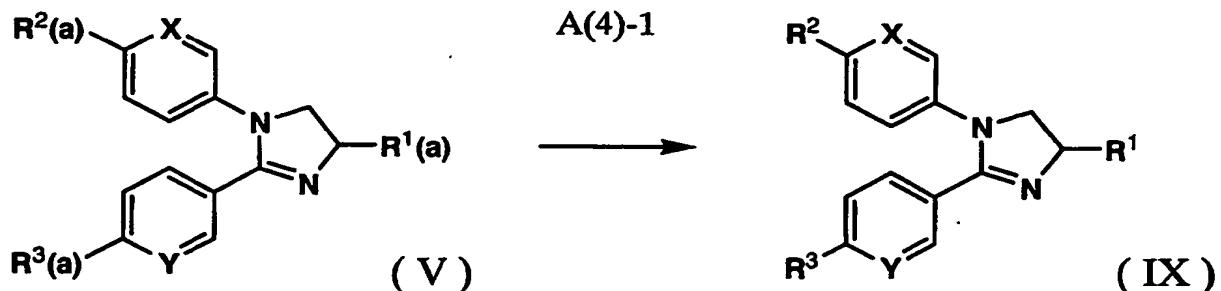
#### Process A(3)



In the above formulae, R represents H, (lower)alkyl or aryl[(lower)alkyl] group, which is not specified. "Tf" represents trifluoromethanesulfonyl as protective group.

5 4,5-Dihydoroimidazole compound (**V**) can be transformed into compound  
**(IX)** by the above mentioned functional group trans formation.

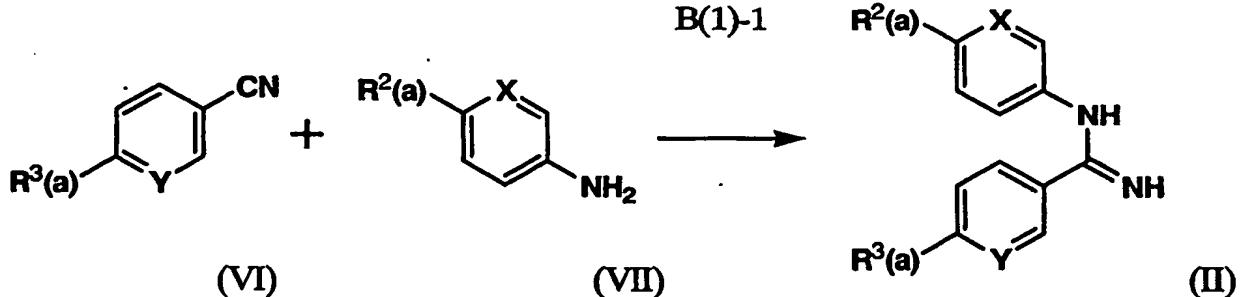
## **Process A(4)**



10 Compound (IX) or pharmaceutically acceptable salts thereof also  
has an inhibiting activity against COX. So compound (IX) or salt thereof  
is also useful as medicament.

Compound (II) can be synthesized from compound (VI) and (VII) by  
15 following process other than purchase.

## **Process B(1)**



In the above formulae,  $R^2(a)$ ,  $R^3(a)$ , X and Y represent the same meanings as defined above.

Process B(1) is the process for preparing the compound (II), which is the starting material of Process A(1) and A(2).

Compound (VI) and (VII) may be purchased if it is commercial, or synthesized according to general methods from commercial compounds, because the compounds as starting compound for synthesis of compound (II) have comparatively simple structure.

5 In this process, first, the solution of compound (VII) is added strong base.

10 The strong base employable in this process is not particularly limited and may include alkali metal hydrides such as lithium hydride, sodium hydride; alkali metal alkoxides such as lithium methoxide, sodium methoxide, sodium ethoxide, potassium t-butoxide; or the like.

15 The solvent employable in this process is not particularly limited so long as it is inactive in this reaction and may include ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane; amides such as N,N-dimethylformamide, dimethylacetamide, hexamethylphosphoric triamide; sulfoxides such as dimethylsulfoxide; or the like.

The reaction temperature varies depending on the starting material, the solvent, etc., but it is usually from -10°C to room temperature, preferably room temperature.

20 The reaction time varies depending on the starting material, the solvent, the reaction temperature, etc., but it is usually from 5min to 1hr, preferably from 10min to 40min.

Preferably, this process is carried out under inert gas such as nitrogen gas.

25 In this process, then the reaction mixture is added compound (VII). The reaction temperature varies depending on the starting material, the solvent, etc., but it is usually from -10°C to room temperature, preferably room temperature.

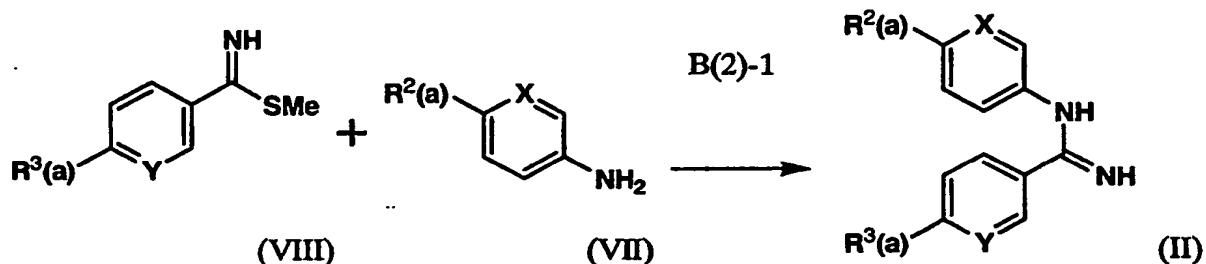
30 The reaction time varies depending on the starting material, the solvent, the reaction temperature, etc., but it is usually from 1hr to 24hrs, preferably from 2hrs to overnight.

After the reaction, the reaction mixture is poured into ice water

to decompose the excess strong base. Then, the desired compound may be collected by filtration as precipitate. Where necessary, it may be washed by solvent such as diisopropyl ether. Further, the desired compound is purified by the conventional method such as silica gel column chromatography, recrystallization, etc, however, it may be used in the next step without further purification.

Compound (II) can be also synthesized from compound (VII) and (VIII) by following process other than purchase.

## 10 Process B(2)



In the above formulae,  $R^2(a)$ ,  $R^3(a)$ , X and Y represent the same meanings as defined above.

15        Process B(2) is the another process for preparing the compound  
      (II), in the case that R<sup>2</sup>(a) is the group such as [(lower)alkoxy]carbonyl  
      or the like, which tends to be nucleophilically attacked more easily  
      than cyano group.

In this process, compound (VII) and (VIII) are condensed in the acidic condition.

Compound (VII) may be purchased if it is commercial, or synthesized according to general methods from commercial compounds.

Compound (VIII) may be synthesized by conventional method, that  
is, first the nitrile compound is led to thioamide compound by  
25 thioacetamide, and then methylated.

The solvent employable in this process is not particularly limited so long as it is inactive in this reaction and may include alcohols such as alcohols such as methanol, ethanol, 2-propanol; ethers such

as diisopropyl ether, tetrahydrofuran, dioxane; and mixed solvent of these; or the like.

The acid for making acidic condition in this process is not particularly limited so long as it is used in a usual reaction as an acid catalyst and may include inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, or the like.

The reaction temperature varies depending on the starting material, the solvent, etc., but it is usually from 50°C to 150°C, preferably reflux condition.

The reaction time varies depending on the starting material, the solvent, the reaction temperature, etc., but it is usually from 30min to 5hrs, preferably from 2hrs to 4hrs.

After the reaction, the reaction mixture is poured into basic water and extracted with organic solvent insoluble with water such as ethyl acetate. The organic layer is dried over anhydrous magnesium sulfate or sodium sulfate, evaporated in vacuo. Where necessary, it may be washed by solvent such as diisopropyl ether. Further, the desired compound is purified by the conventional method such as silica gel column chromatography, recrystallization, etc, however, it may be used in the next step without further purification.

Above processes (Process A and B), all starting materials and product compounds may be salts. The compounds of above processes can be converted to salt according to a conventional method.

For therapeutic purpose, the compound (I) and a pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compounds as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, inhalant,

suppositories, solution, lotion, suspension, emulsion, ointment, gel, cream, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

5

And on the commercial package comprising the pharmaceutical composition mentioned above and a written matter, which states above mentioned effects, is also useful.

10        While the dosage of therapeutically effective amount of the compound (I) will vary depending upon the age and condition of each individual patient, an average single dose of about 0.01 mg, 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound (I) may be effective for treating the above-mentioned diseases. In general, 15 amounts between 0.01 mg/body and about 1,000 mg/body may be administered per day.

The patents, patent applications and publications cited herein are incorporated by reference.

20

#### THE BEST MODE FOR CARRYING OUT THE INVENTION...

The following Examples are given only for the purpose of illustrating the present invention in more detail.

25        Example 1-1

#### N<sup>1</sup>-(4-Bromophenyl)-4-methoxybenzamidine

Under Nitrogen gas, to a solution of 4-bromoaniline (3.88g, 22.5mmol) in dimethylsulfoxide (30ml) was added NaH (568mg, 23.7mmol) 30 at room temperature. After the mixture was stirred for 30min, 4-methoxybenzonitrile (3.0g, 22.5mmol) was added.

The reaction mixture was stirred overnight then poured into 300ml

of ice-water. The precipitate was collected by filtration and washed with isopropyl ether to give 5.53g of desired compound as a white solid (80.4%).

5 IR (KBr, cm<sup>-1</sup>) : 3473, 3357, 2958, 1612, 1249, 1174, 1103, 1074, 1030, 837.

NMR (DMSO-d<sub>6</sub>, δ) : 3.80(3H, s), 6.32(2H, brs), 6.78(2H, d, J=9Hz), 6.96(2H, d, J=9Hz), 7.42(1H, d, J=8Hz), 7.92(2H, d, J=8Hz).

MS : 305 (M+H)<sup>+</sup> (<sup>79</sup>Br), 307 (M+H)<sup>+</sup> (<sup>81</sup>Br).

10

#### Example 1-2

1-(4-Bromophenyl)-2-(4-methoxyphenyl)-4-trifluoromethyl-1H-imidazole

15 To a mixture of N<sup>1</sup>-(4-Bromophenyl)-4-methoxybenzamidine obtained by Example 1-1 (2.0g, 6.55mmol) and sodium bicarbonate (826mg, 9.83mmol) in 2-propanol (20ml) was added 3-bromo-1,1,1-trifluoro-2-propanone (2.0g, 10.5mmol). The reaction mixture was heated at 80°C for 2hrs.

The reaction mixture was cooled to room temperature and filtered.

20 The organic layer was evaporated in vacuo. The residue in acetic acid (20ml) was heated at 110°C for 2.5hrs.

The reaction mixture was poured into ice-water (100ml) and neutralized with sodium hydroxide aq. and extracted with ethyl acetate (50ml). The organic layer was washed with brine, dried by magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography (20g) eluting with n-hexane/ethyl acetate (10/1) and washed with diisopropylether to give 660mg of desired compound (25.4%).

30 MP : 140-141°C.

IR (KBr, cm<sup>-1</sup>) : 3140, 2970, 1487, 1294, 1252, 1149, 1122, 1026, 833.

NMR (DMSO-d<sub>6</sub>, δ) : 3.75(3H, s), 6.92(2H, d, J=9Hz), 7.27(2H, d, J=9Hz),

7.36(2H, d, J=9Hz), 7.71(2H, d, J=2Hz), 8.18(1H, s).

MS : 397 (M+H)<sup>+</sup> (<sup>79</sup>Br), 399 (M+H)<sup>+</sup> (<sup>81</sup>Br).

**Example 2-1**

5      **4-Methoxy-N<sup>1</sup>-(2-Methoxy-5-pyridinyl)benzamidine**

Reaction was carried out in a manner similar to Example 1-1 using 4-methoxybenzonitrile and 5-amino-2-methoxypyridine to give 4.57g of desired compound (78.8%).

10

IR (KBr, cm<sup>-1</sup>) : 3452, 3334, 3205, 2946, 1606, 1483, 1273, 1246, 1176, 1028, 841.

NMR (DMSO-d<sub>6</sub>, δ) : 3.80(3H, s), 3.82(3H, s), 6.36(2H, brs), 6.76(1H, d, J=9Hz), 6.96(2H, d, J=9Hz), 7.20(1H, dd, J=9Hz and 3Hz), 7.67(1H, d, J=3Hz), 7.94(2H, d, J=9Hz).

15      MS : 258 (M+H)<sup>+</sup>.

**Example 2-2**

20      **2-(4-Methoxyphenyl)-1-(2-methoxy-5-pyridinyl)-4-trifluoromethyl-1H-imidazole hydrochloride**

Reaction was carried out in a manner similar to Example 1-2 using 4-methoxy-N<sup>1</sup>-(2-Methoxy-5-pyridinyl)benzamidine obtained by Example 2-1 to give 2-(4-methoxyphenyl)-1-(2-methoxy-5-pyridinyl)-4-trifluoromethyl-1H-imidazole.

And then the product obtained was dissolved in ethyl acetate and treated with 4N hydrogen chloride in ethyl acetate to give 399mg of desired compound as a white amorphous solid (14.7%).

30      NMR (DMSO-d<sub>6</sub>, δ) : 3.75(3H, s), 3.89(3H, s), 6.80-7.05(3H, m), 7.31(2H, d, J=9Hz), 7.43(1H, d, J=9Hz), 7.74(1H, dd, J=9Hz and 2Hz), 8.17(1H, s), 8.27(1H, s).

MS : 350 (M+H)<sup>+</sup> (free).

Example 3-1

N<sup>1</sup>-(4-Methoxyphenyl)-2-methoxy-5-amidinopyridine

5

Under Nitrogen gas, to a solution of p-anisidine (2.75g, 22.4mmol) in tetrahydrofuran (15ml) was added dropwise 1.0M sodium bis(trimethylsilyl)amide in tetrahydrofuran (23.5ml, 23.5mmol) at room temperature. After the mixture was stirred for 20min,

10 6-methoxynicotinonitrile (3.0g, 22.4mmol) was added.

The reaction mixture was stirred for 4hrs, then poured into 300ml of ice-water. The precipitate was collected by filtration, washed with diisopropyl ether to give 3.36g of desired compound (58.4%) (mixture).

This material was used without further purification.

15

NMR (DMSO-d<sub>6</sub>, δ) : 3.73(3H, s), 3.90(3H, s), 6.27(2H, brs), 6.70-7.00(5H, m), 8.24(1H, dd, J=9Hz and 2Hz), 8.72(1H, d, J=2 Hz).

MS : 258 (M+H)<sup>+</sup>.

20 Example 3-2

1-(4-Methoxyphenyl)-2-(2-methoxy-5-pyridinyl)-4-trifluoromethyl-1H-imidazole

Reaction was carried out in a manner similar to Example 1-2 using  
25 N<sup>1</sup>-4-methoxy-2-methoxy-5-amidinopyridine obtained by Example 3-1 to give 526.6mg of desired compound as a colorless crystal (21.5%).

MP : 90-92°C.

IR (KBr, cm<sup>-1</sup>) : 3141, 3107, 1604, 1518, 1294, 1248, 1159, 1118, 835.

30 NMR (DMSO-d<sub>6</sub>, δ) : 3.81(3H, s), 3.83(3H, s), 6.81(1H, d, J=9Hz), 7.05(2H, d, J=9Hz), 7.38(2H, d, J=9Hz), 7.65(1H, dd, J=9Hz and 2Hz), 8.08(1H, d, J=2Hz), 8.17(1H, s).

MS : 350 (M+H)<sup>+</sup>.

Example 4-1

4-Cyano-4,5-dihydro-1-(4-methoxyphenyl)-2-(2-methoxy-5-pyridinyl)-  
5 1H-imidazole

To a suspension of N<sup>1</sup>-4-Methoxy-2-methoxy-5- amidinopyridine obtained by Example 3-1 in tetrahydrofuran (20ml) were added 2-chloroacrylonitrile and diisopropylethylamine successively. The 10 reaction mixture was heated at 70°C. After 5hrs, an additional 1.07ml of 2-chloroacrylonitrile was added and refluxed overnight.

The reaction mixture was cooled to room temperature, filtered and the solvent was removed in vacuo. The crude mixture was purified by silica gel column chromatography (24g) eluting with ethyl acetate to 15 give 460mg of desired compound (54.9%).

This material was used in Example 4-2 without further purification.

Example 4-2

4-Cyano-1-(4-methoxyphenyl)-2-(2-methoxy-5-pyridinyl)-1H-imidazole

A suspension of the residue obtained by Example 4-1 and manganese(IV) oxide (MnO<sub>2</sub>) (1.3g, 10eq) in toluene (10ml) was heated at 85°C for 5.5hrs. To the reaction mixture was added manganese(IV) oxide (0.65g, 5eq) and heated at 110°C for 3hrs.

After cooling, the mixture was filtered through a Celite. The organic fraction was concentrated (396mg). The crude mixture was purified by silica gel column chromatography (12g) eluting with chloroform/methanol (50/1→15/1) and washed with diisopropyl ether to give 200.8mg of desired compound as a colorless solid (24.1%, through 30 Example 4-1 and 4-2).

MP : 130-132°C.

IR (KBr, cm<sup>-1</sup>) : 3132, 2949, 2233, 1604, 1516, 1466, 1292, 1254, 1024, 835.

NMR (DMSO-d<sub>6</sub>, δ) : 3.81(3H, s), 3.84(3H, s), 6.81(1H, d, J=9Hz), 7.06(2H, d, J=9Hz), 7.37(2H, d, J=9Hz), 7.62(1H, dd, J=9Hz and 2Hz), 8.10(1H, d, J=2Hz), 8.47(1H, s).

MS : 307 (M+H)<sup>+</sup>.

**Example 5-1**

**N<sup>1</sup>-(4-Benzylxyphenyl)-2-methoxy-5-amidinopyridine**

10

Reaction was carried out in a manner similar to Example 3-1 using 4-benzylxyaniline hydrochloride to give 8.7g of desired compound (71.7%).

15 IR (KBr, cm<sup>-1</sup>) : 3488, 3396, 3031, 2958, 1635, 1502, 1373, 1236, 1103, 1020, 840.

NMR (DMSO-d<sub>6</sub>, δ) : 3.90(3H, s), 5.06(2H, s), 6.28(2H, brs), 6.70-7.05(5H, m), 7.25-7.60(5H, m), 8.24(1H, dd, J=9Hz and 2Hz), 8.72(1H, d, J=2Hz).  
MS : 334 (M+H)<sup>+</sup>.

20

**Example 5-2**

**1-(4-Benzylxyphenyl)-2-(2-methoxy-5-pyridinyl)-4-trifluoromethyl-1H-imidazole**

25 Reaction was carried out in a manner similar to Example 1-2 using N<sup>1</sup>-(4-Benzylxyphenyl)-2-methoxy-5-amidinopyridine obtained by Example 5-1 to give 2.27g of desired compound (44.5%).

IR (KBr, cm<sup>-1</sup>) : 3064, 2950, 1290, 1244, 1157, 1122, 1022, 835.

30 NMR (DMSO-d<sub>6</sub>, δ) : 3.84(3H, s), 5.16(2H, s), 6.81(1H, d, J=9Hz), 7.05-7.58(9H, m), 7.65(1H, dd, J=9Hz and 2Hz), 8.08(1H, d, J=2Hz), 8.17(1H, s).

MS : 426 (M+H)<sup>+</sup>.

**Example 6**

1-(4-Hydroxyphenyl)-2-(2-methoxy-5-pyridinyl)-4-trifluoromethyl-1H  
5 -imidazole

To a solution of

1-(4-benzyloxyphenyl)-2-(2-methoxy-5-pyridinyl)-  
4-trifluoromethyl-1H-imidazole obtained by Example 5-2 (2.25g,

10 5.29mmol) in cyclohexene (22ml) and ethanol (45ml) was added 20%  
palladium hydroxide on carbon (550mg). The resulting mixture was  
stirred at reflux for 2hrs.

After cooling to room temperature, the mixture was filtered through  
Celite and washed with ethanol. The filtrate was concentrated in vacuo,  
15 and then the residue was washed with diisopropyl ether to give 1.31g  
of desired compound as a white solid (73.9%).

MP : 198-200°C.

IR (KBr, cm<sup>-1</sup>) : 3600-2600, 1469, 1292, 1247, 1159, 1126, 833.

20 NMR (CDCl<sub>3</sub>, δ) : 3.91(3H, s), 6.67(1H, brs), 6.73(1H, d, J=9Hz), 6.87(2H,  
d, J=9Hz), 7.11(2H, d, J=9Hz), 7.43(1H, s), 7.86(1H, dd, J=9Hz and 2Hz),  
8.03(1H, d, J=2Hz).

MS : 336 (M+H)<sup>+</sup>.

25 **Example 7**

2-(2-Methoxy-5-pyridinyl)-1-(4-trifluoromethanesulfonyloxyphenyl)-  
4-trifluoromethyl-1H-imidazole

To the mixture of 1-(4-hydroxyphenyl)-2-(2-methoxy-5-pyridinyl)-  
30 4-trifluoromethyl-1H-imidazole obtained by Example 6 (600mg, 1.79mmol)  
and triethylamine (190mg, 1.88mmol) in chloroform (12ml) was added  
trifluoromethanesulfonic anhydride dropwise at an ice bath temperature

and stirred for 4.5hrs.

Sodiumhydrogencarbonate aq. (10ml) was added to quench the reaction. The reaction mixture was partitioned between chloroform and water. The organic layer was washed with water and then brine, dried by magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography (10g) eluting with n-hexane/ethyl acetate (10/1) to give 593mg of desired compound (70.9%).

IR (KBr, cm<sup>-1</sup>) : 3118, 3062, 1421, 1255, 1219, 1136, 891.

10 NMR (CDCl<sub>3</sub>, δ) : 3.92(3H, s), 6.71(1H, d, J=9Hz), 7.30-7.48(4H, m), 7.50(1H, s), 7.66(1H, dd, J=9Hz and 2Hz), 8.08(1H, d, J=2Hz).  
MS : 467 (M+H)<sup>+</sup>.

#### Example 8

15 1-(4-Cyanophenyl)-2-(2-methoxy-5-pyridinyl)-4-trifluoromethyl-1H-imidazole

To a solution of 2-(2-methoxy-5-pyridinyl)-1-(4-trifluoromethanesulfonyloxyphenyl)-4-trifluoromethyl-1H-imidazole obtained by Example 7 (150mg, 0.321mmol) in N,N-dimethylformamide (7.5ml) were added zinc cyanide (Zn(CN)<sub>2</sub>) (38mg, 0.321mmol) and tetrakis(triphenylphosphine)palladium (Pd(PPh<sub>3</sub>)<sub>4</sub>) (185mg, 0.16mmol) at ambient temperature under nitrogen gas. The mixture was stirred at 85°C for 2days.

25 The mixture was cooled to room temperature and partitioned between ethyl acetate (50ml) and water (50ml). The organic layer was washed with water and brine, then dried by magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography (20g) eluting with toluene/ethyl acetate (10:1) and washed with diisopropyl ether to give 57.2mg of desired compound as a white solid (51.8%).

MP : 155-158°C.

IR (KBr, cm<sup>-1</sup>) : 3120, 2250, 1606, 1250, 1122, 822.

NMR (DMSO-d<sub>6</sub>, δ) : 3.85(3H, s), 6.82(1H, d, J=9Hz), 7.61(1H, dd, J=9Hz and 2Hz), 7.65(2H, d, J=9Hz), 8.03(2H, d, J=9Hz), 8.12(1H, d, J=2Hz), 8.36(1H, s).

MS : 345 (M+H)<sup>+</sup>.

**Example 9**

4-Ethoxycarbonyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

ole

A mixture of N<sup>1</sup>-(4-methoxyphenyl)-4-methoxybenzamidine (0.65 g), ethyl bromopyruvate (0.64 ml) and sodium hydrogencarbonate (0.85 g) in ethanol (7 ml) was stirred at reflux condition for overnight.

After cooling to room temperature, the reaction mixture was filtrated and evaporated in vacuo. Then the residue was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (5/1→2/1) to give 244mg of desired compound as an oil (27.3%).

IR (Neat, cm<sup>-1</sup>) : 3437, 3392, 3367, 3217, 3140, 3072, 2966, 2843, 1803, 1699, 1651, 1614.

NMR (DMSO-d<sub>6</sub>, δ) : 1.29(3H, t, J=7.1Hz), 3.74(3H, s), 3.80(3H, s), 4.27(2H, q, J=7.1Hz), 6.88(2H, dd, J=6.8Hz and 2.1Hz), 7.02(2H, dd, J=6.7Hz and 2.1Hz), 7.26 (2H, dd, J=5.0Hz and 2.1Hz), 7.28 (2H, dd, J=6.7Hz and 2.1Hz), 8.02 (1H, s).

MS : 353 (M+H)<sup>+</sup>.

**Example 10**

4-Carbamoyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

A mixture of 4-ethoxycarbonyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 9 (244mg) and sodium methoxide (112mg) in formamide (2ml) was stirred at 100°C for 2hrs.

After cooling to room temperature, the reaction mixture was poured 5 into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (1/1→0/1) to give 73mg of desired compound (32.6%).

10 MP : 167-169°C.

IR (KBr, cm<sup>-1</sup>): 3427, 3342, 3276, 3155, 2964, 2841, 1672, 1610.

NMR (DMSO-d<sub>6</sub>, δ) : 3.74(3H, s), 3.80(3H, s), 6.87-6.89(2H, m), 7.00-7.03(2H, m), 7.20(1H, s), 7.26-7.29(4H, m), 7.43(1H, s), 7.77(1H, s).

15 MS : 324 (M+H)<sup>+</sup>.

#### Example 11

4-Cyano-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole hydrochloride

20 A mixture of 4-carbamoyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 10 (73mg) and phosphorus oxychloride (63μl) in N,N-dimethylformamide (1ml) was stirred at room temperature for 1hr.

25 The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (2/1).

After correcting the fraction, the solvent was removed by evaporation and the residue was dissolved in ethyl acetate (1ml). 4N Hydrochloride/ethyl acetate (56ml) was added to the above solution. Resulting precipitates were corrected by filtration and washed with

isopropyl ether to give 38mg of desired compound (49.2%).

MP : 142-143°C.

IR (KBr, cm<sup>-1</sup>): 3425, 3407, 3132, 3076, 3043, 3026, 2962, 2929, 2835,

5 2231, 1608.

NMR (DMSO-d<sub>6</sub>, δ) : 3.74(3H, s), 3.80(3H, s), 6.55(1H, s), 6.88-6.91(2H, m), 7.03-7.05(2H, m), 7.25-7.32(4H, m), 8.39(1H, s).

MS : 306 (free) (M+H)<sup>+</sup>.

10 Example 12-1

4-Cyano-4,5-dihydro-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

A mixture of N<sup>1</sup>-(4-methoxyphenyl)-4-methoxybenzamidine (5g),

15 2-chlorocyanooethylene (2.01ml) and N,N-diisopropylethylamine (4.38 ml) in tetrahydrofuran (100ml) was stirred at reflux condition for 6hrs. Additional 2-chlorocyanooethylene (2.01ml) was added, the mixture was refluxed for overnight.

20 After cooling to room temperature, the reaction mixture was evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (1/1) to give 3.28 g of desired compound as an oil (63.7%).

25 IR (Neat, cm<sup>-1</sup>) : 3283, 3217, 3114, 3055, 3003, 2958, 2839, 2243, 2048, 1896, 1732, 1606.

NMR (DMSO-d<sub>6</sub>, δ) : 3.70(3H, s), 3.74(3H, s), 4.11-4.19(2H, m), 5.20(1H, dd, J=10.5Hz and 8.2Hz), 6.81-6.97(6H, m), 7.32-7.37(2H, m).

MS : 308 (M+H)<sup>+</sup>.

30 Example 12-2

4-Cyano-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

A suspension of 4-cyano-4,5-dihydro-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 12-1 (2.7g) and manganese(IV) oxide ( $MnO_2$ ) (3.82 g) in N,N-dimethylformamide (30ml) was stirred at 100°C for 4hrs.

5 After filtration, the reaction mixture was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. To the solution of the residue in N,N-dimethylformamide (30ml), phosphorus oxychloride (2.46ml) was added under stirring at 0°C.

10 After stirring at room temperature for 1hr, the reaction mixture was poured into saturated aqueous sodium hydrogencarbonate and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo to give 2.11g of desired compound (78.7%).

15 MP : 132-134°C.

NMR (DMSO- $d_6$ ,  $\delta$ ) : 3.74(3H, s), 3.80(3H, s), 6.87-6.93(2H, m), 7.02-7.08(2H, m), 7.23-7.34(4H, m), 8.39(1H, s).

MS : 306 ( $M+H$ )<sup>+</sup>.

20 Example 13

4-Cyano-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole hydrochloride

25 4N Hydrochloride/ethyl acetate (254 $\mu$ l) was added to a solution of 4-cyano-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 12-2 (300mg) in ethyl acetate (1ml). Resulting precipitates were corrected by filtration and washed with isopropyl ether to give 300mg of desired compound (86.4%).

30 MP : 142-143°C.

IR (KBr,  $cm^{-1}$ ) : 3425, 3407, 3132, 3076, 3043, 3026, 2962, 2929, 2835, 2231, 1608.

NMR (DMSO-d<sub>6</sub>, δ) : 3.74(3H, s), 3.80(3H, s), 6.55(1H, s), 6.88-6.91(2H, m), 7.03-7.05(2H, m), 7.25-7.32(4H, m), 8.39(1H, s).  
MS : 306 (free) (M+H)<sup>+</sup>.

5 Example 14

4-Ethoxycarbonyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

A mixture of 4-cyano-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole (315mg) and 4N hydrochloride/ethanol (6.2ml) was stirred at reflux condition for 1hr.

After cooling to room temperature, the reaction mixture was poured into saturated aqueous sodium hydrogencarbonate and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (1/1) to give 0.26g of desired compound (71.5%).

MP : 142-143°C.

IR (Neat, cm<sup>-1</sup>) : 3437, 3392, 3367, 3217, 3140, 3072, 2966, 2843, 1803, 1699, 1651, 1614.

NMR (DMSO-d<sub>6</sub>, δ) : 1.29(3H, t, J=7.1Hz), 3.74(3H, s), 3.80(3H, s), 4.27(2H, q, J=7.1Hz), 6.88(2H, dd, J=6.8Hz and 2.1Hz), 7.02(2H, dd, J=6.7Hz and 2.1Hz), 7.26(2H, dd, J=5.0Hz and 2.1Hz), 7.28(2H, dd, J=6.7Hz and 2.1Hz), 8.02(1H, s).

MS : 353 (M+H)<sup>+</sup>.

Example 15

4-Hydroxymethyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

30

1N Diisopropylaluminiumhydride in toluene (3.76ml) was added dropwise to a solution of 4-ethoxycarbonyl-1-(4-methoxyphenyl)-2-(4-

methoxyphenyl)-1H-imidazole obtained by Example 14 (5ml) under stirring at -78°C, and stirred at -78°C for 2hrs.

The reaction mixture was quenched by sat. ammonium chloride aq., then 1N hydrochloric acid was added and extracted with water. The combined aqueous layer was neutralized with sat. sodium hydrogencarbonate aq., and extracted with ethyl acetate, dried over magnesium sulfate. After evaporation of the solution, the residue was purified by silicagel column chromatography eluting with n-hexane/ethyl acetate (1/1) to give 0.14g of desired compound (30%).

10

IR (Neat, cm<sup>-1</sup>) : 3369, 3307, 3224, 3076, 3006, 2939, 2837, 1676, 1608.

NMR (DMSO-d<sub>6</sub>, δ) : 3.73(3H, s), 3.79(3H, s), 4.42(2H, d, J=5.6Hz), 4.96(1H, t, J=5.6Hz), 6.85(2H, d, J=8.8Hz), 7.00(2H, d, J=8.9Hz), 7.15-7.25(5H, m).

15 MS : 311 (M+H)<sup>+</sup>.

#### Example 16

##### 4-Formyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

20 Dimethylsulfoxide (125μl) was added to a solution of oxalylchloride (118μl) in dichloromethane (2ml) under stirring at -78°C. After stirred at -78°C for 10min, a solution of 4-hydroxymethyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 15 (0.21g) in dichloromethane (2ml) was added and stirred at -78°C for 1hr.

25 Triethylamine (0.66ml) was added to the reaction mixture, and stirred at 0°C for 20min.

The mixture was quenched by sat. ammonium chloride aq., and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo to give 120mg of desired compound as an oil (57.5%).

30

IR (Neat, cm<sup>-1</sup>) : 3126, 3057, 3005, 2960, 2837, 2760, 2551, 2048, 1685, 1610.

NMR (CDCl<sub>3</sub>, δ) : 3.83(3H, s), 3.86(3H, s), 6.81(2H, dd, J=6.9Hz and 2.0Hz), 6.94(2H, dd, J=6.8Hz and 2.1Hz), 7.16(2H, dd, J=6.7Hz and 2.2Hz), 7.36(2H, dd, J=6.7Hz and 2.1Hz), 7.16(1H, s), 9.98(1H, s).  
MS : 309 (M+H)<sup>+</sup>.

5

Example 17

4-Difluoromethyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole hydrochloride

10 Diethylaminosulfur trifluoride (154μl) was added to a solution of 4-formyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 16 (120mg) in dicloromethane (2ml) under stirring at 0°C.

15 After stirring at room temperature for overnight, the reaction mixture was poured into saturated aqueous sodium hydrogencarbonate and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (1/1). After correcting the fraction, the solvent was removed by evaporation and 20 the residue was dissolved in ethyl acetate (1ml). 4N hydrochloride/ethyl acetate (97μl) was added. Resulting precipitates were corrected by filtration and washed with isopropyl ether to give 24mg of desired compound (16.8%).

25 MP : 150-153°C.

IR (KBr, cm<sup>-1</sup>) : 3454, 3433, 3265, 3101, 3060, 2958, 2837, 2735, 2659, 2563, 1606.

30 NMR (DMSO-d<sub>6</sub>, δ) : 3.76(3H, s), 3.80(3H, s), 6.84(1H, t, J=56.2Hz), 6.91-6.97(2H, s), 7.02-7.08(2H, m), 7.28-7.38(4H, m), 7.93 (1H, t, J=2.2Hz).

MS : 331 (free) (M+H)<sup>+</sup>.

**Example 18**

**4-Carboxy-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole**

A mixture of 4-cyano-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole (1.5g) in 50% sulfuric acid (16ml) was stirred at reflux condition for 1hr.

After cooling to room temperature, the reaction mixture was poured into 6% sodium hydroxide aq. (100ml), and washed with ethyl acetate. The aqueous layer was acidified by conc. hydrochloric acid and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The resulting precipitates were corrected by filtration and washed with isopropyl ether to give 1.18g of desired compound (74.1%).

MP : 102-105°C.

IR (KBr, cm<sup>-1</sup>) : 3427, 3269, 3174, 3141, 3086, 3005, 2965, 2910, 2839, 1678, 1610.

NMR (DMSO-d<sub>6</sub>, δ) : 3.76(3H, s), 3.813(3H, s), 6.89(2H, dt, J=7.0Hz and 2.0Hz), 7.03(2H, dt, J=7.2Hz and 2.0Hz), 7.26-7.32(4H, m), 7.97(1H, s).

MS : 325 (M+H)<sup>+</sup>.

**Example 19**

**4-Ethylmethycarbamoyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole**

A mixture of 4-carboxy-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 18 (170mg), N-ethylmethylamine (45 μl), 1-hydroxybenzotriazole (71mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (100mg) in N,N-dimethylformamide (5ml) was stirred at room temperature for overnight.

The reaction mixture was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The

residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (1/1). The resulting precipitates were corrected by filtration and washed with isopropyl ether to give 72mg of desired compound (37.6%).

5

MP : 138-139 °C.

IR (KBr, cm<sup>-1</sup>) : 3124, 3068, 3006, 2966, 2929, 2841, 1603.

NMR (DMSO-d<sub>6</sub>, δ) : 1.05-1.29(3H, m), 2.91-3.03(2H, m), 3.33-3.56(2H, m), 3.74(3H, s), 3.80(3H, s), 3.91-4.06(1H, m), 6.88(2H, dt, J=8.8Hz and 1.8Hz), 7.02(2H, dt, J=8.8Hz and 2.0Hz), 7.23-7.30(4H, m), 7.72(1H, s).

10 MS : 366 (M+H)<sup>+</sup>.

#### Example 20

15 4-Cyclopropyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole hydrochloride

20 A mixture of N<sup>1</sup>-(4-methoxyphenyl)-4-methoxybenzamidine (1g), 2-bromo-1-cyclopropylethanone (1.27g) and sodium hydrogencarbonate (656mg) in 2-propanol (10ml) was stirred at reflux condition for overnight.

25 After cooling to room temperature, the reaction mixture was filtered off and evaporated in vacuo. Then the residue was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was dissolved in acetic acid (10ml), and refluxed for 1hr.

30 After cooling to room temperature, the mixture was poured into saturated sodium hydrogencarbonate aq. and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (3/1). After correcting the fraction, the solvent was removed by evaporation and the residue was dissolved in ethyl acetate (5ml).

4N hydrochloride/ethyl acetate (175 $\mu$ l) was added. Resulting precipitates were corrected by filtration and washed with isopropyl ether to give 200mg of desired compound (14.4%).

5 MP : 180-181°C.  
IR (KBr, cm<sup>-1</sup>) : 3273, 3051, 2966, 2935, 2906, 2835, 2740, 2640, 2592, 1610.  
NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 0.88-0.96(2H, m), 1.00-1.07(2H, m), 2.02-2.11(2H, m), 3.79(3H, s), 3.80(3H, s), 7.00-7.11(4H, m), 7.35-7.41(4H, m), 10 7.67(1H, s).  
MS : 321 (free) (M+H)<sup>+</sup>.

**Example 21**

15 **1-(4-Methoxyphenyl)-2-(4-methoxyphenyl)-4-methyl-1H-imidazole hydrochloride**

20 85mg of desired compound was obtained from N<sup>1</sup>-(4-methoxyphenyl)-4-methoxybenzamidine (200mg) and 1-bromoacetone (204 $\mu$ l) in the similar manner to that of Example 20.

MP : 203-205°C.  
IR (KBr, cm<sup>-1</sup>) : 3400, 3114, 3055, 2966, 2929, 2833, 2804, 2711, 2650, 2578, 2426, 1612.  
NMR (DMSO-d<sub>6</sub>,  $\delta$ ) : 2.39(3H, s), 3.79(3H, s), 3.81(3H, s), 7.02-7.12(4H, m), 7.36-7.66(4H, m), 7.66(1H, s), 14.6-15.5(1H, br).  
MS : 295 (free) (M+H)<sup>+</sup>.

**Example 22-1**

25 **N<sup>1</sup>-(4-Ethoxycarbonylphenyl)-4-methoxybenzamidine**

30 A mixture of methyl 4-methoxybenzenecarbimidothioate hydroiodide (3.9g), ethyl 4-aminobenzoate (2.08g) and acetic acid (2ml) in

2-propanol (40ml) was stirred at reflux condition for 2hrs.

After cooling to room temperature, the reaction mixture was poured into saturated sodium hydrogencarbonate aq. and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo.

5 Resulting precipitates were corrected by filtration and washed with isopropyl ether to give 2.35g of desired compound (62.4%).

MP : 128-132°C.

IR (KBr, cm<sup>-1</sup>) : 3456, 3305, 3251, 3178, 2976, 2933, 2850, 1711, 1626.

10 NMR (DMSO-d<sub>6</sub>, δ) : 1.31(3H, t, J=7.1Hz), 3.81(3H, s), 4.28(2H, q, J=7.1Hz), 6.46(2H, s), 6.90-7.01(4H, m), 7.86-7.91(4H, m).

MS : 299 (M+H)<sup>+</sup>.

Example 22-2

15 1-(4-Ethoxycarbonylphenyl)-2-(4-methoxyphenyl)-4-trifluoromethyl-1H-imidazole

A mixture of N<sup>1</sup>-(4-Ethoxycarbonylphenyl)-4-methoxybenzamidine obtained by Example 22-1 (0.5g), 3-bromo-1,1,1-trifluoro-2-propanone 20 (0.35ml) and sodium hydrogencarbonate (563mg) in 2-propanol (5ml) was stirred at reflux condition for 4hrs.

After cooling to room temperature, the reaction mixture was filtered off and evaporated in vacuo. Then the residue was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and 25 evaporated in vacuo. The residue was dissolved in acetic acid (10ml), and refluxed for 1hr.

After cooling to room temperature, the mixture was poured into saturated sodium hydrogencarbonate aq. and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was 30 purified by silicagel column chromatography eluting with n-hexane/ethyl acetate (3/1) to give 0.53g of desired compound as an oil (81%).

IR (Neat, cm<sup>-1</sup>) : 3745, 3610, 3435, 3396, 3365, 3298, 3280, 3236, 3130, 2962, 2927, 2856, 1693, 1649.

NMR (DMSO-d<sub>6</sub>, δ) : 1.33(3H, t, J=7.1Hz), 3.75(3H, s), 4.34(2H, q, J=7.1Hz), 6.91(2H, dd, J=6.9Hz and 1.9Hz), 7.26(2H, dd, J=6.8Hz and 2.0Hz), 7.53  
5 (2H, dd, J=6.8Hz and 1.7Hz), 8.04 (2H, dd, J=6.7Hz and 1.8Hz), 8.25 (1H, d, J=1.2Hz).

MS : 391 (M+H)<sup>+</sup>.

### Example 23

10 1-(4-Carbamoylphenyl)-2-(4-methoxyphenyl)-4-trifluoromethyl-1H-imidazole

25 255mg of desired compound was obtained from  
1-(4-ethoxycarbonylphenyl)-2-(4-methoxyphenyl)-4-trifluoromethyl-1H-imidazole obtained by Example 22-2 (710mg) in the similar manner to  
that of Example 10.

IR (KBr, cm<sup>-1</sup>) : 3410, 3303, 3190, 3122, 2960, 2841, 1655, 1614.

NMR (DMSO-d<sub>6</sub>, δ) : 3.77(3H, s), 6.90(2H, dt, J=8.8Hz and 2.0Hz), 7.26(2H,  
20 dt, J=8.8Hz and 2.1Hz), 7.46(2H, d, J=8.5Hz), 7.52(1H, s), 7.96(2H,  
d, J=8.5Hz), 8.10(1H, s), 8.21(1H, d, J=1.2Hz).

MS : 362 (M+H)<sup>+</sup>.

### Example 24

25 1-(4-Cyanophenyl)-2-(4-methoxyphenyl)-4-trifluoromethyl-1H-imidazole

A mixture of 1-(4-carbamoylphenyl)-2-(4-methoxyphenyl)-4-trifluoromethyl-1H-imidazole obtained by Example 23 (200mg) and  
30 phosphorus oxychloride (0.16ml) in N,N-dimethylformamide (2ml) was stirred at room temperature for 1hr.

The reaction mixture was poured into saturated sodium

hydrogencarbonate aq. and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. Resulting precipitates were corrected by filtration and washed with isopropyl ether to give 171mg of desired compound (90%).

5

MP : 146-148°C.

IR (KBr, cm<sup>-1</sup>) : 3415, 3163, 3118, 3064, 3012, 2968, 2906, 2839, 2229, 1608.

NMR (DMSO-d<sub>6</sub>, δ) : 3.76(3H, s), 6.92(2H, dt, J=8.9Hz and 1.9Hz), 7.25(2H, dt, J=8.7Hz and 2.0Hz), 7.60(2H, dt, J=8.5Hz and 1.8Hz), 8.00(2H, dt, J=8.6Hz and 1.7Hz), 8.27(1H, d, J=1.1Hz).

MS : 344 (M+H)<sup>+</sup>.

Example 25-1

15 4-Cyano-4,5-dihydro-1-(4-ethoxycarbonylphenyl)-2-(4-methoxyphenyl)-1H-imidazole

20 265mg of desired compound was obtained from N<sup>1</sup>-(4-ethoxycarbonylphenyl)-4-methoxybenzamidine (500 mg) in the similar manner to that of Example 12-1.

IR (Neat, cm<sup>-1</sup>) : 3417, 3253, 3217, 3068, 2974, 2902, 2841, 1711, 1603.

NMR (DMSO-d<sub>6</sub>, δ) : 1.28(3H, t, J=7.1Hz), 3.78(3H, s), 4.26(2H, q, J=7.1Hz), 4.31-4.46(2H, m), 5.27(1H, t, J=9.9Hz), 6.88-6.97(4H, m), 7.37(2H, dt, J=8.8Hz and 1.9Hz), 7.79 (2H, dt, J=8.7Hz and 1.9Hz).

25 MS : 350 (M+H)<sup>+</sup>.

Example 25-2

4-Cyano-1-(4-ethoxycarbonylphenyl)-2-(4-methoxyphenyl)-1H-imidazol

30 e

A suspension of 4-cyano-4,5-dihydro-1-(4-ethoxycarbonylphenyl)-

2-(4-methoxyphenyl)-1H-imidazole obtained by Example 25-1 (0.26g) and manganese(IV) oxide ( $MnO_2$ ) (259 mg) in ethyl acetate (5 ml) was stirred at reflux condition for overnight.

After filtration, the reaction mixture was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (5/1) to give 117mg of desired compound (45.3%).

MP : 139-140°C.

IR (KBr,  $cm^{-1}$ ) : 3425, 3143, 3060, 2979, 2947, 2902, 2839, 2235, 1718, 1606.

NMR (DMSO- $d_6$ ,  $\delta$ ) : 1.33(3H, t,  $J=7.1Hz$ ), 3.75(3H, s), 4.34(2H, q,  $J=7.1Hz$ ), 6.90(2H, dt,  $J=8.8Hz$  and  $1.9Hz$ ), 7.25(2H, dt,  $J=8.8Hz$  and  $1.9Hz$ ), 7.52(2H, dt,  $J=8.5Hz$  and  $1.7Hz$ ), 8.05(2H, dt,  $J=8.5Hz$  and  $1.7Hz$ ), 8.55(1H, s).

MS : 348 ( $M+H$ )<sup>+</sup>.

#### Example 26

1-(4-Carbamoylphenyl)-4-cyano-2-(4-methoxyphenyl)-1H-imidazole

49mg of desired compound was obtained from 4-cyano-1-(4-ethoxycarbonylphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 25-2 (100mg) in the similar manner to that of Example 10 (53.5%).

MP : 228-290 °C.

IR (KBr,  $cm^{-1}$ ) : 3456, 3396, 3354, 3292, 3172, 3113, 3051, 2970, 2837, 2227, 1682, 1612.

NMR (DMSO- $d_6$ ,  $\delta$ ) : 3.75(3H, s), 6.91(2H, d,  $J=8.8Hz$ ), 7.26(2H, d,  $J=8.8Hz$ ), 7.46(2H, d,  $J=8.5Hz$ ), 7.54(1H, s), 7.97(2H, d,  $J=8.5Hz$ ), 8.11(1H, s), 8.52(1H, s).

MS : 319 ( $M+H$ )<sup>+</sup>.

Example 27

4-Cyano-1-(4-cyanophenyl)-2-(4-methoxyphenyl)-1H-imidazole

24mg of desired compound was obtained from 1-(4-carbamoylphenyl)-

5 4-Cyano-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 26  
(40mg) in the similar manner to that of Example 24 (63.6%).

MP : 185-186 °C

IR (KBr, cm<sup>-1</sup>) : 3419, 3219, 3132, 3091, 3057, 3012, 2968, 2935, 2837,

10 2229, 1608.

NMR (DMSO-d<sub>6</sub>, δ) : 3.76(3H, s), 6.92(2H, d, J=8.8Hz), 7.25(2H, d, J=8.7Hz),  
7.59(2H, d, J=8.5Hz), 8.02(2H, d, J=8.5Hz), 8.56(1H, s).

MS : 301 (M+H)<sup>+</sup>.

15 Example 28

4-Acetyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

3N solution of methylmagnesium bromide in diethyl ether (1.17ml) was added to a solution of 4-cyano-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole (357mg) in tetrahydrofuran (5ml).

20 After stirring at room temperature for 2hrs, the reaction mixture was poured into hydrochloric acid and extracted with ethyl acetate, washed with water, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting 25 with n-hexane/ethyl acetate (5/1) to give 258mg of desired compound (68.5%).

MP : 116-117°C

IR (KBr, cm<sup>-1</sup>) : 3431, 3118, 3066, 3008, 2964, 2929, 2837, 1668, 1610.

30 NMR (DMSO-d<sub>6</sub>, δ) : 2.48(3H, s), 3.74(3H, s), 3.80(3H, s), 6.89(2H, d, J=8.6Hz), 7.03(2H, d, J=8.8Hz), 7.26-7.31(4H, m), 8.12(1H, s).

MS : 323 (M+H)<sup>+</sup>.

Example 29-1

4-Ethoxycarbonyl-4,5-dihydro-1-(4-benzyloxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

5

A mixture of N<sup>1</sup>-(4-benzyloxyphenyl)-4-methoxybenzamidine (1.25g), ethyl 2-chloroacrylate (0.76g) and N,N-diisopropylethylamine (0.98ml) in tetrahydrofuran (12ml) was stirred at reflux condition for 2hrs.

10 After cooling to room temperature, the reaction mixture was filtered off and the filtrate was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo.

This material was used in the next step without further purification.

Example 29-2

15 4-Ethoxycarbonyl-1-(4-benzyloxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

The residue of Example 29-1 was dissolved in N,N-dimethylformamide (10ml), and manganese(IV) oxide (1.63g) was added to the solution.

20 After stirring at 100°C for 4hrs, the reaction mixture was cooled to room temperature and poured into water and ethyl acetate. After filtration, the mixture was extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (1/1) to give 1.5g of desired compound as an oil (93.1%).

IR (Neat, cm<sup>-1</sup>) : 3433, 3253, 3224, 3140, 3064, 2966, 2843, 1722, 1712, 1606.

NMR (DMSO-d<sub>6</sub>, δ) : 1.29(3H, t, J=7.1Hz), 3.75(3H, s), 4.27(2H, d, J=7.1Hz), 5.15(2H, s), 6.88(2H, dt, J=8.9Hz and 1.9Hz), 7.10(2H, dt, J=8.9Hz and 1.9Hz), 7.24-7.49(9H, m), 8.04(1H, s).

MS : 429 (M+H)<sup>+</sup>.

Example 30

1-(4-Benzylxyphenyl)-4-formyl-2-(4-methoxyphenyl)-1H-imidazole

5        0.95N Diisopropylaluminiumhydride in toluene (6.49ml) was added dropwise to a solution of 4-ethoxycarbonyl-1-(4-benzylxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 29-2 (0.88g) in dichloromethane (5ml) under stirring at -78°C, and stirred at -78°C for 2hrs.

10      The reaction mixture was quenched by sat. ammonium chloride aq., then 1N hydrochloric acid was added and extracted with water. After sodium hydroxide aq. was added, extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo.

15      The residue was dissolved in N,N-dimethylformamide (10ml), and manganese(IV) oxide (1.79g) was added to the solution.

20      After stirring at 100°C for 1hr, the reaction mixture was cooled to room temperature and poured into water and ethyl acetate. After filtration, the mixture was extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (1/1) to give 0.77g of desired compound as an oil (97.5%).

IR (Neat, cm<sup>-1</sup>) : 3440, 3361, 3219, 3124, 3062, 2937, 2837, 2760, 1732, 1684, 1610.

25      NMR (DMSO-d<sub>6</sub>, δ) : 3.75(3H, s), 5.16(2H, s), 6.89(2H, dt, J=8.9Hz and 1.9Hz), 7.12(2H, dt, J=8.9Hz and 2.1Hz), 7.27-7.49(9H, m), 8.28(1H, s), 9.82(1H, s).

MS : 385 (M+H)<sup>+</sup>.

30      Example 31

1-(4-Benzylxyphenyl)-4-difluoromethyl-2-(4-methoxyphenyl)-1H-imidazole

Diethylaminosulfur trifluoride (0.46 ml) was added to a solution of 1-(4-benzyloxyphenyl)-4-formyl-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 30 (0.45g) in dichloromethane (5ml) under stirring at 0°C.

After stirring at room temperature for overnight, the reaction mixture was poured into saturated aqueous sodium hydrogencarbonate and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (1/1) to give 0.38g of desired compound as an oil (79.9%).

IR (Neat,  $\text{cm}^{-1}$ ) : 3433, 3155, 3113, 3066, 3041, 2964, 2841, 1732, 1610.

NMR ( $\text{DMSO-d}_6$ ,  $\delta$ ) : 3.74(3H, s), 5.15(2H, s), 6.87(2H, d,  $J=8.9\text{Hz}$ ), 7.08(1H, t,  $J=55.0\text{Hz}$ ), 7.10(2H, d,  $J=8.9\text{Hz}$ ), 7.24-7.45(9H, m), 7.73(1H, t,  $J=2.3\text{Hz}$ ).

MS : 407 ( $\text{M+H}^+$ ).

### Example 32

4-Difluoromethyl-1-(4-hydroxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

A suspension of 1-(4-benzyloxyphenyl)-4-difluoromethyl-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 31 (0.38g) and dry 20% palladium hydroxide on carbon ( $\text{Pd(OH)}_2/\text{C}$ ) (100mg) in ethanol (8ml) and cyclohexene (4ml) was stirred at reflux condition for 1hr and cooled to room temperature.

After filtration, the reaction mixture was evaporated in vacuo to give 0.3g of desired compound (ca.100%).

MP : 143-145°C

IR (KBr,  $\text{cm}^{-1}$ ) : 3149, 3111, 3003, 2966, 2837, 2804, 2679, 2602, 1610.

NMR (DMSO-d<sub>6</sub>, δ) : 3.74(3H, s), 6.80-6.91(4H, m), 6.96(1H, t, J=55.0Hz), 7.14(2H, dt, J=8.7Hz and 1.9Hz), 7.27(2H, dt, J=8.9Hz and 1.9Hz), 7.68(1H, t, J=2.2Hz), 9.90(1H, s).

MS : 317 (M+H)<sup>+</sup>.

5

**Example 33**

**4-Difluoromethyl-2-(4-methoxyphenyl)-1-(4-trifluoromethanesulfonyloxyphenyl)-1H-imidazole**

10        Triethylamine (0.15ml) and trifluoromethanesulfonic anhydride (0.18ml) was added to a solution of 4-difluoromethyl-1-(4-hydroxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 32 (300mg) in chloroform (5ml) under stirring at 0°C.

15        After stirring at 0°C for 4hrs, the reaction mixture was poured into saturated aqueous sodium hydrogencarbonate and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (1/1) to give 0.24g of desired compound as an oil (56.4%).

20

IR (Neat, cm<sup>-1</sup>) : 3159, 3118, 3078, 3006, 2939, 2848, 1610.

NMR (DMSO-d<sub>6</sub>, δ) : 3.74(3H, s), 6.89(2H, dt, J=8.9Hz and 1.9Hz), 7.01(1H, t, J=54.8Hz) 7.23(2H, dt, J=8.9Hz and 2.0Hz), 7.54-7.69(4H, m), 7.92(1H, t, J=2.3Hz).

25        MS : 449 (M+H)<sup>+</sup>.

**Example 34**

**1-(4-Cyanophenyl)-4-difluoromethyl-2-(4-methoxyphenyl)-1H-imidazole**

30

A suspension of 4-difluoromethyl-2-(4-methoxyphenyl)-1-(4-trifluoromethanesulfonyloxyphenyl)-1H-imidazole obtained by Example

33 (0.2g) , zinc cyanide ( $Zn(CN)_2$ ) (55mg) and tetrakis(triphenylphosphine)palladium ( $Pd(PPh_3)_4$ ) (272mg) in N,N-dimethylformamide (1ml) was stirred at 85°C for overnight under nitrogen atmosphere then cooled to room temperature.

5 After filtration, the reaction mixture was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (1/1) to give 83mg of desired compound (47.7%).

10

MP : 131-132°C.

IR (KBr,  $cm^{-1}$ ) : 3222, 3157, 3114, 2966, 2839, 2231, 1610.

NMR (DMSO- $d_6$ ,  $\delta$ ) : 3.75(3H, s), 6.91(2H, dt,  $J=8.9Hz$  and  $1.9Hz$ ), 7.02(1H, t,  $J=54.8Hz$ ), 7.24(2H, dt,  $J=8.8Hz$  and  $2.0Hz$ ), 7.55 (2H, dt,  $J=8.7Hz$  and  $1.7Hz$ ), 7.93(1H, t,  $J=2.2Hz$ ), 7.95(2H, dt,  $J=8.5Hz$  and  $2.0Hz$ ).  
15 MS : 326 ( $M+H$ )<sup>+</sup>.

Example 35-1

1-(4-Benzylxyphenyl)-4,5-dihydro-4-ethoxycarbonyl-2-(2-methoxy-5-pyridinyl)-1H-imidazole  
20

2.67g of desired compound was obtained from a mixture of N<sup>1</sup>-(4-benzylxyphenyl)-2-methoxy-5-amidinopyridine (2.57g) and ethyl 2-chloacrylate (1.56g) in the similar manner to that of Example 12-1  
25 (80.3%).

IR (Neat,  $cm^{-1}$ ) : 3448, 3411, 3378, 3037, 2981, 2949, 2902, 1734, 1608.  
NMR (DMSO- $d_6$ ,  $\delta$ ) : 1.24(3H, t,  $J=7.1Hz$ ), 3.83(3H, s), 4.06(2H, d,  $J=9.9Hz$ ),  
4.17(2H, q,  $J=7.1Hz$ ), 4.81(1H, t,  $J=9.8Hz$ ), 5.04(2H, s), 6.77(1H, d,  
30  $J=8.6Hz$ ), 6.93(4H, s), 7.29-7.44(5H, m), 7.68(1H, dd,  $J=8.6Hz$  and  $2.4Hz$ ),  
8.18(1H, d,  $J=2.4Hz$ ).  
MS : 432 ( $M+H$ )<sup>+</sup>.

Example 35-2

1-(4-Benzylxyphenyl)-4-ethoxycarbonyl-2-(2-methoxy-5-pyridinyl)-1H-imidazole

5

1.74g of desired compound was obtained from a suspension of 1-(4-benzylxyphenyl)-4,5-dihydro-4-ethoxycarbonyl-2-(2-methoxy-5-pyridinyl)-1H-imidazole obtained by Example 35-1 (2.67g) in N,N-dimethylformamide (27ml) in the similar manner to that of Example 10 25-2 (65.5%).

MP : 109-110°C.

IR (KBr, cm<sup>-1</sup>) : 3433, 3390, 3136, 3070, 2976, 2941, 2841, 1693, 1608.

NMR (DMSO-d<sub>6</sub>, δ) : 1.29(3H, t, J=7.1Hz), 3.84(3H, s), 4.28(2H, q, J=7.1Hz), 15 5.15(2H, s), 6.80(1H, d, J=8.6Hz), 7.12(2H, d, J=8.9Hz), 7.32-7.49(7H, m), 7.65(1H, dd, J=8.6Hz and 2.4Hz), 8.06(1H, d, J=2.4Hz), 8.12(1H, s).

MS : 430 (M+H)<sup>+</sup>.

20 Example 36

1-(4-Benzylxyphenyl)-4-formyl-2-(2-methoxy-5-pyridinyl)-1H-imidazole

0.83g of desired compound was obtained from 1-(4-benzylxyphenyl)-25 4-ethoxycarbonyl-2-(2-methoxy-5-pyridinyl)-1H-imidazole (1.46g) in the similar manner to that of Example 30 (63.3%).

IR (Neat, cm<sup>-1</sup>) : 3217, 3126, 3059, 2947, 2831, 2760, 1687, 1606.

NMR (DMSO-d<sub>6</sub>, δ) : 3.84(3H, s), 5.16(2H, s), 6.82(1H, d, J=8.5Hz), 30 7.14(2H, dt, J=8.9Hz and 2.0Hz), 7.35-7.50(7H, m), 7.66(1H, dd, J=8.6Hz and 2.5Hz), 8.11(1H, d, 2.3Hz), 8.35(1H, s), 9.84(1H, s).

MS : 386 (M+H)<sup>+</sup>.

Example 37

1-(4-Benzylxyphenyl)-4-difluoromethyl-2-(2-methoxy-5-pyridinyl)-1H-imidazole

5

0.48g of desired compound was obtained from 1-(4-benzylxyphenyl)-4-formyl-2-(2-methoxy-5-pyridinyl)-1H-imidazole obtained by Example 36 (0.83g) in the similar manner to that of Example 29-1 (54.7%).

10

IR (Neat,  $\text{cm}^{-1}$ ) : 3429, 3209, 3151, 3064, 3028, 2979, 2949, 2875, 2549, 1734, 1604.

15

NMR (DMSO- $d_6$ ,  $\delta$ ) : 3.84(3H, s), 5.15(2H, s), 6.80(1H, d,  $J=8.5\text{Hz}$ ), 7.00(1H, t,  $J=54.8\text{Hz}$ ), 7.12(2H, d,  $J=9.0\text{Hz}$ ), 7.27-7.49(7H, m), 7.63(1H, dd,  $J=8.6\text{Hz}$  and  $2.5\text{Hz}$ ), 7.81(1H, t,  $J=2.2\text{Hz}$ ), 8.07(1H, d,  $J=1.8\text{Hz}$ ).  
MS : 408 ( $M+H$ )<sup>+</sup>.

Example 38

4-Difluoromethyl-1-(4-hydroxyphenyl)-2-(2-methoxy-5-pyridinyl)-1H-imidazole

20

0.48g of desired compound was obtained from 1-(4-benzylxyphenyl)-4-difluoromethyl-2-(2-methoxy-5-pyridinyl)-1H-imidazole obtained by Example 37 (0.48 g) in the similar manner to that of Example 32 (ca.100%).

25

MP : 155-156°C.

IR (KBr,  $\text{cm}^{-1}$ ) : 3012, 2962, 2808, 2681, 2603, 1603.

30

NMR (DMSO- $d_6$ ,  $\delta$ ) : 3.83(3H, s), 6.77-6.86(3H, m), 6.99(1H, t,  $J=54.9\text{Hz}$ ), 7.19(2H, d,  $J=8.8\text{Hz}$ ), 7.63(1H, dd,  $J=8.7\text{Hz}$  and  $2.5\text{Hz}$ ), 7.76(1H, t,  $J=2.2\text{Hz}$ ), 8.06(1H, d,  $J=2.4\text{Hz}$ ), 10.06(1H, br).  
MS : 318 ( $M+H$ )<sup>+</sup>.

**Example 39**

**4-Difluoromethyl-2-(2-methoxy-5-pyridinyl)-1-(4-trifluoromethanesulfonyloxyphenyl)-1H-imidazole**

5       0.2g of desired compound was obtained from 4-difluoromethyl-1-(4-hydroxyphenyl)-2-(2-methoxy-5-pyridinyl)-1H-imidazole obtained by Example 38 (0.17g) in the similar manner to that of Example 33(83.1%).

10      IR (Neat, cm<sup>-1</sup>) : 3429, 3224, 3165, 3084, 3020, 2958, 2860, 1724, 1664, 1604.

NMR (DMSO-d<sub>6</sub>, δ) : 3.84(3H, s), 6.80(2H, d, J=8.4Hz), 7.03(1H, t, J=54.8Hz), 7.56-7.71(4H, m), 7.99(1H, t, J=2.2Hz), 8.09(1H, d, J=2.4Hz).  
MS : 450 (M+H)<sup>+</sup>.

15      **Example 40**

**1-(4-Cyanophenyl)-4-difluoromethyl-2-(2-methoxy-5-pyridinyl)-1H-imidazole**

20      62mg of desired compound was obtained from 4-difluoromethyl-2-(2-methoxy-5-pyridinyl)-1-(4-trifluoromethanesulfonyloxyphenyl)-1H-imidazole obtained by Example 39 (0.2g) in the similar manner to that of Example 34 (42.7%).

MP : 160-161°C.

25      IR (KBr, cm<sup>-1</sup>) : 3219, 3140, 3101, 3051, 3005, 2985, 2954, 2241, 1608.  
NMR (DMSO-d<sub>6</sub>, δ) : 3.85(3H, s), 6.82(1H, d, J=8.6Hz), 7.04(1H, t, J=54.7Hz), 7.57-7.63(3H, m), 7.99-8.03(3H, m), 8.11(1H, d, J=2.3Hz).  
MS : 327 (M+H)<sup>+</sup>.

30      **Example 41-1**

**4-Ethoxycarbonyl-4,5-dihydro-1-(4-methoxyphenyl)-2-(2-methoxy-5-pyridinyl)-1H-imidazole**

5.41g of desired compound was obtained from a mixture of  
N<sup>1</sup>-(4-methoxyphenyl)-2-methoxy-5-amidinopyridine (5g) and ethyl  
2-chloroacrylate (3.92g) in the similar manner to that of Example 12-1  
5 (78.3%).

IR (Neat, cm<sup>-1</sup>) : 3448, 3429, 3411, 3381, 3047, 2981, 2951, 2904, 2841,  
1736, 1608.

NMR (DMSO-d<sub>6</sub>, δ) : 1.24(3H, t, J=7.1 Hz), 3.73(3H, s), 3.83(3H, s),  
10 4.05(2H, d, J=9.5Hz), 4.17(2H, q, J=7.1Hz), 4.81(1H, t, J=9.5Hz),  
6.77(1H, d, J=8.5Hz), 6.79-6.96(4H, m), 7.67(1H, dd, J=8.6Hz and 2.4Hz),  
8.17(1H, d, J=2.3Hz).

MS : 356 (M+H)<sup>+</sup>.

15 Example 41-2

4-Ethoxycarbonyl-1-(4-methoxyphenyl)-2-(2-methoxy-5-pyridinyl)-1H-imidazole

3.71g of desired compound was obtained from a suspension of  
20 4-ethoxycarbonyl-4,5-dihydro-1-(4-methoxyphenyl)-2-(2-methoxy-5-pyridinyl)-1H-imidazole obtained by Example 41-1 (5.41g) in  
N,N-dimethylformamide (54ml) in the similar manner to that of Example  
25-2 (69%).

25 MP : 135-137 °C.

IR (KBr, cm<sup>-1</sup>) : 3413, 3224, 3145, 3070, 2949, 2902, 2837, 1703, 1610.

NMR (DMSO-d<sub>6</sub>, δ) : 1.29(3H, t, J=7.1Hz), 3.81(3H, s), 3.83(3H, s),  
4.28(2H, q, J=7.1Hz), 6.80(1H, d, J=8.6Hz), 7.04(2H, dt, J=8.9Hz and  
2.0Hz), 7.34(2H, dt, J=8.9Hz and 2.2Hz), 7.64(1H, dd, J=8.6Hz and 2.5Hz),  
30 8.06(1H, d, J=2.4Hz), 8.11(1H, s).

MS : 354 (M+H)<sup>+</sup>.

**Example 42**

**4-Formyl-1-(4-methoxyphenyl)-2-(2-methoxy-5-pyridinyl)-1H-imidazole**

5       0.88g of desired compound was obtained from 4-ethoxycarbonyl-1-(4-methoxyphenyl)-2-(2-methoxy-5-pyridinyl)-1H-imidazole obtained by Example 41-2 (1.7g) in the similar manner to that of Example 30 (59.1%).

IR (Neat, cm<sup>-1</sup>) : 3435, 3367, 3134, 3074, 3006, 2960, 2846, 1682, 1608.

10     NMR (DMSO-d<sub>6</sub>, δ) : 3.81(3H, s), 3.84(3H, s), 6.82(1H, d, J=8.5Hz), 7.06(2H, dt, J=8.9Hz and 1.9Hz), 7.37(2H, dt, J=8.9Hz and 1.9Hz), 7.65(1H, dd, J=8.6Hz and 2.5Hz), 8.11(1H, d, J=2.1Hz), 8.34(1H, s), 9.84(1H, s).

MS : 310 (M+H)<sup>+</sup>.

15

**Example 43**

**4-Difluoromethyl-1-(4-methoxyphenyl)-2-(2-methoxy-5-pyridinyl)-1H-imidazole**

20       332mg of desired compound was obtained from 4-formyl-1-(4-methoxyphenyl)-2-(2-methoxy-5-pyridinyl)-1H-imidazole obtained by Example 42 (0.83g) in the similar manner to that of Example 31 (36.5%).

MP : 106-107 °C.

25     IR (KBr, cm<sup>-1</sup>) : 3398, 3153, 3114, 2997, 2947, 2844, 1606.

NMR (DMSO-d<sub>6</sub>, δ) : 3.81(3H, s), 3.83(3H, s), 6.80(1H, d, J=8.8Hz), 7.00(1H, t, J=54.9Hz), 7.04(2H, dt, J=8.9Hz and 2.1Hz), 7.33(2H, dt, J=8.8Hz and 2.1Hz), 7.63(1H, dd, J=8.6Hz and 2.5Hz), 7.80(1H, t, J=2.3Hz), 8.07(1H, d, J=2.4Hz).

30     MS : 332 (M+H)<sup>+</sup>.

**Example 44**

**4-Ethoxycarbonyl-1-(4-methoxyphenyl)-2-(2-methoxy-5-pyridinyl)-1H-imidazole**

1.5g of desired compound was obtained from a suspension of  
5  $N^1$ -(4-methoxyphenyl)-2-methoxy-5-amidinopyridine (1.5g) in  
2-propanol (10ml) in the similar manner to that of Example 9 (72.8%).

**Example 45**

**1-(4-Benzylxyphenyl)-4-carboxy-2-(4-methoxyphenyl)-1H-imidazole**

10 To a solution of 4-ethoxycarbonyl-1-(4-benzylxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 29-2 (1.46g) in ethanol (10ml) and tetrahydrofuran (10ml), 1N aqueous sodium hydroxide (6.81ml) was added.

15 After stirring at room temperature overnight, the reaction mixture was poured into water and ethyl acetate, and extracted with water. Then, the water layer was acidified with 1N hydrochloric acid, extracted with ethyl acetate, dried over magnesium sulfate, and evaporated in vacuo. The resulting precipitates were collected by filtration and washed with  
20 diisopropyl ether to give the target compound (1.1g).

MP : 113-115°C.

1H NMR (200MHz, DMSO-d<sub>6</sub>, δ) : 3.75(3H, s), 5.15(2H, s), 6.88(2H, d, J=8.8Hz), 7.10(2H, d, J=8.9Hz), 7.24-7.45(9H, m), 7.96(1H, s),  
25 11.0-12.5(1H, br).

IR (KBr, cm<sup>-1</sup>) : 3392, 3224, 3145, 3076, 2972, 2935, 2893, 1701, 1610.

**Example 46**

**1-(4-Benzylxyphenyl)-4-(N-ethyl-N-methylcarbamoyl)-2-(4-methoxyphenyl)-1H-imidazole**

A mixture of 1-(4-benzylxyphenyl)-4-carboxy-2-(4-methoxyphenyl)-1H-

imidazole obtained by Example 45 (0.44g), ethylmethylamine (118ml), 1-hydroxybenzotriazole (186mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (263mg) in N,N-dimethylformamide (5ml) was stirred at room temperature overnight.

5       The reaction mixture was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica-gel column chromatography eluting with (n-Hexane:Ethyl acetate=1:1). The resulting precipitates were corrected by filtration and washed with diisopropyl ether to give the  
10 target compound (0.44g).

MP : 118-119°C.

1H NMR (DMSO-d<sub>6</sub>, δ) : 1.06-1.28(3H, m), 2.91-3.02(2H, m), 3.40-3.54(2H, m), 3.74(3H, s), 3.93-4.07(1H, m), 5.15(2H, s), 6.88(2H, d, J=8.8Hz), 7.10(2H, d, J=8.9Hz), 7.24-7.30(4H, m), 7.36-7.49(5H, m), 7.73(1H, s).  
15      IR (KBr, cm<sup>-1</sup>) : 3124, 3066, 2958, 2935, 2839, 1608.  
Mass m/e : 442 (M<sup>+</sup>+1).

#### Example 47

20      4-(N-Ethyl-N-methylcarbamoyl)-1-(4-hydroxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

The target compound was obtained from 1-(4-benzyloxyphenyl)-4-(N-ethyl-N-methylcarbamoyl)-2-(4-methoxyphenyl)-1H-imidazole obtained  
25      by Example 46 in the similar manner to that of Example 62 described later.

1H NMR (DMSO-d<sub>6</sub>, δ) : 1.10-1.28(3H, m), 2.90-3.02(2H, m), 3.40-3.50(2H, m), 3.74(3H, s), 3.91-4.03(1H, m), 6.82(2H, d, J=8.7Hz), 6.88(2H, d, J=8.9Hz), 7.11(1H, s), 7.14(2H, d, J=8.7Hz), 7.27(2H, d, J=8.7Hz), 7.67(1H, s).  
30

IR (KBr, cm<sup>-1</sup>) : 3126, 3091, 3018, 2968, 2933, 2831, 2738, 2677, 2600,

2476, 1612.

MS m/e : 352 (M<sup>+</sup>+1).

**Example 48**

5      **1-(4-Benzylxyphenyl)-4-(N,N-diethylcarbamoyl)-2-(4-methoxyphenyl)-1H-imidazole**

The target compound was obtained from 1-(4-benzylxyphenyl)-4-carboxy-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 45 and  
10      N,N-diethylamine in the similar manner to that of Example 46.

MP : 146-147°C.

1H NMR (DMSO-d<sub>6</sub>, δ) : 1.10-1.30(6H, m), 3.38-3.50(2H, m), 3.74(3H, s), 3.85-4.02(2H, m), 5.15(2H, s), 6.88(2H, d, J=8.8Hz), 7.10(2H, d, J=8.9Hz), 7.24-7.30(4H, m), 7.36-7.49(5H, m), 7.72(1H, s).  
15      IR (KBr, cm<sup>-1</sup>) : 3113, 2972, 2929, 1593.

MS m/e : 456 (M<sup>+</sup>+1).

**Example 49**

20      **4-(N,N-Diethylcarbamoyl)-1-(4-hydroxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole**

The target compound was obtained from 1-(4-benzylxyphenyl)-4-(N,N-diethylcarbamoyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by  
25      Example 48 in the similar manner to that of Example 62 described later.

1H NMR (DMSO-d<sub>6</sub>, δ) : 1.02-1.30(6H, m), 3.22-3.48(2H, m), 3.73(3H, s), 3.83-4.02(2H, m), 6.81-6.92(4H, m), 7.14(2H, dd, J=6.7Hz, 2.0Hz), 7.27(2H, dt, J=9.4Hz, 2.5Hz), 7.66(1H, s).

30      IR (KBr, cm<sup>-1</sup>) : 3145, 3030, 2970, 2937, 2833, 1693, 1606.  
MS m/e : 366 (M<sup>+</sup>+1).

**Example 50**

**1-(4-Benzylxyphenyl)-2-(4-methoxyphenyl)-4-(1-piperidinecarbonyl)-1H-imidazole**

5       The target compound (0.5g) was obtained from 1-(4-benzylxyphenyl)-4-carboxy-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 45 and piperidine in the similar manner to that of Example 46.

10       $^1\text{H}$  NMR (200MHz, DMSO-d<sub>6</sub>,  $\delta$ ) : 1.507-1.572(4H, m), 1.605-1.67(2H, m), 3.462-3.644(2H, m), 3.74(3H, s), 3.918-4.244(2H, m), 5.144(2H, s), 6.879(2H, d, J=4.5Hz), 7.096(2H, d, J=4.5Hz), 7.251(2H, d, J=4.3Hz), 7.278(2H, d, J=4.3Hz), 7.348-7.478(5H, m), 7.721(1H, s).  
IR (KBr, cm<sup>-1</sup>) : 3116, 3033, 2931, 2850.  
MS m/e : 468 (M+H)<sup>+</sup>.

15

**Example 51**

**1-(4-Hydroxyphenyl)-2-(4-methoxyphenyl)-4-(1-piperidinecarbonyl)-1H-imidazole**

20       The target compound (0.41g) was obtained from 1-(4-benzylxyphenyl)-2-(4-methoxyphenyl)-4-(1-piperidinecarbonyl)-1H-imidazole obtained by Example 50 in the similar manner to that of Example 62 described later.

25       $^1\text{H}$  NMR (200MHz, DMSO-d<sub>6</sub>,  $\delta$ ) : 1.509-1.577(4H, m), 1.611-1.674(2H, m), 3.51-3.657(2H, m), 3.734(3H, s), 4.035-4.224(2H, m), 6.814(2H, d, J=4.4Hz), 6.881(2H, d, J=4.3Hz), 7.136(2H, d, J=4.4Hz), 7.256(2H, d, J=4.4Hz), 7.668(1H, s), 9.908(1H, bs).  
IR (KBr, cm<sup>-1</sup>) : 3151, 3035, 2935, 2852, 1606.  
30      MS m/e : 378 (M+H)<sup>+</sup>.

**Example 52-1**

**N<sup>1</sup>-(4-Benzylxyphenyl)-4-methoxybenzamidine**

To a solution of 4-benzylxyaniline hydrochloride (3g) in tetrahydrofuran (15ml), 1.0M sodium bis(trimethylsilyl)amide in tetrahydrofuran (26.7ml) was added dropwise at room temperature. After the mixture was stirred for 20min, anisonitrile (1.69g) was added.

The reaction mixture was stirred for 4hrs, and then poured into 300ml of ice-water. The precipitate was collected by filtration, washed with diisopropyl ether to give the target compound (3.3g).

10

<sup>1</sup>H NMR (200MHz, DMSO-d<sub>6</sub>, δ) : 3.8(3H, s), 5.05(2H, s), 6.09(2H, bs), 6.74-6.8(2H, m), 6.96(4H, d, J=8.5Hz), 7.29-7.49(5H, m), 7.92(2H, d, J=8.9Hz).

MS m/e : 333 (M+H)<sup>+</sup>.

15

**Example 52-2**

**4-Cyano-4,5-dihydro-1-(4-benzylxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole**

20 A mixture of N<sup>1</sup>-(4-Benzylxyphenyl)-4-methoxybenzamidine obtained by Example 52-1 (2g), 2-chlorocyanooethylene (0.36ml) and N,N-diisopropylethylamine (0.79ml) in tetrahydrofuran (10ml) was stirred at reflux condition overnight.

25 After cooling to room temperature, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water and brine, then dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica-gel column chromatography eluting with (n-Hexane:Ethyl acetate=1:1) to give the target compound (0.82g).

30

MP : 121-122°C.

<sup>1</sup>H NMR (200MHz, DMSO-d<sub>6</sub>, δ) : 3.74(3H, s), 4.11-4.19(2H, m), 5.03(2H,

s), 5.16-5.25(1H, m), 6.87(2H, d, J=9Hz), 6.93(4H, s), 7.29-7.44(7H, m).

MS (ESI<sup>+</sup>) m/e : 384 (M+H)<sup>+</sup>.

5      Example 52-3

**4-Cyano-1-(4-benzyloxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole**

A suspension of 4-cyano-4,5-dihydro-1-(4-benzyloxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 52-2 (0.8g) and manganese(IV) oxide (0.91g) in N,N-dimethylformamide (8ml) was stirred at 100°C for 4hrs.

After filtration, the reaction mixture was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. To the solution of the residue in N,N-dimethylformamide (8ml), phosphorus oxychloride (0.58ml) was added under stirring at 0°C.

After stirring at room temperature for 2hrs, the reaction mixture was poured into saturated aqueous sodiumhydrogencarbonate and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica-gel column chromatography eluting with (n-Hexane:Ethyl acetate=3:1 to 1:1) to give the target compound (0.74g) as an oil.

1H NMR (200MHz, DMSO-d<sub>6</sub>, δ) : 3.75(3H, s), 5.16(2H, s), 6.89(2H, d, J=8.5Hz), 7.12(2H, d, J=9Hz), 7.25-7.48(9H, m), 8.4(1H, s).

MS (ESI<sup>+</sup>) m/e : 382 (M+H)<sup>+</sup>.

Example 53

**4-Cyano-1-(4-hydroxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole**

30

The target compound was obtained from 4-cyano-1-(4-benzyloxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by

Example 52-3 in the similar manner to that of Example 62 described later.

1H NMR (CDCl<sub>3</sub>, δ) : 3.74(3H, s), 6.75-6.95(4H, m), 7.10-7.35(4H, m), 8.36(1H, s), 9.98(1H, bs).

5 MS (ESI, m/e) : 292 (M+1).

Example 54-1

1-(4-Benzylxyphenyl)-4-cyano-4,5-dihydro-2-(2-methoxy-5-pyridinyl)-1H-imidazole

10

The target compound was obtained from N<sup>1</sup>-(4-Benzylxyphenyl)-2-methoxy-5-pyridinyl amidine in the similar manner to that of Example 52-2.

15 1H NMR (200MHz, DMSO-d<sub>6</sub>, δ) : 3.84(3H, s), 4.15-4.21(2H, m), 5.05(2H, s), 5.25(1H, dd, J=8.8, 10.5Hz), 6.78(1H, d, J=8.5Hz), 6.92-7.04(4H, m), 7.32-7.45(5H, m), 7.66(1H, dd, J=2.5, 8.5Hz), 8.19(1H, d, J=2Hz).  
MS (ESI<sup>+</sup>) m/e : 385 (M+H)<sup>+</sup>.

20 Example 54-2

1-(4-Benzylxyphenyl)-4-cyano-2-(2-methoxy-5-pyridinyl)-1H-imidazole

25 The target compound was obtained from 1-(4-Benzylxyphenyl)-4-cyano-4,5-dihydro-2-(2-methoxy-5-pyridinyl)-1H-imidazole obtained by Example 54-1 in the similar manner to that of Example 52-3.

30 1H NMR (200MHz, DMSO-d<sub>6</sub>, δ) : 3.84(3H, s), 5.16(2H, s), 6.81(1H, d, J=8Hz), 7.14(2H, d, J=9Hz), 7.316-7.5(7H, m), 7.63(1H, dd, J=2.3, 8.5Hz), 8.1(1H, dd, J=2.5Hz), 8.47(1H, s).  
MS (ESI<sup>+</sup>) m/e : 383 (M+H)<sup>+</sup>.

Example 55

1-(4-Benzylxyphenyl)-4-ethylcarbonyl-2-(2-methoxy-5-pyridinyl)-1H-imidazole

5 To a solution of 1-(4-benzylxyphenyl)-4-cyano-2-(2-methoxy-5-pyridinyl)-1H-imidazole obtained by Example 54-2 (1.1g) in tetrahydrofuran (10ml), 1N solution of ethylmagnesium bromide in tetrahydrofuran (8.63ml) was added under stirring at 0°C.

10 After stirring at room temperature for 1hr, the reaction mixture was poured into aqueous 10% potassium hydrogen sulfate and stirred at room temperature for 30min. The mixture was alkalinized with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate, washed with water, dried over magnesium sulfate and evaporated in vacuo. The resulting precipitates were collected by filtration and washed with 15 diisopropyl ether to give the target compound (1.07g).

MP : 126-128°C.

1H NMR (DMSO-d<sub>6</sub>, δ) : 1.10(3H, t, J=7.4Hz), 2.95(2H, q, J=7.4Hz), 3.84(3H, s), 5.16(2H, s), 6.81(1H, d, J=8.6Hz), 7.12(2H, d, J=8.9Hz), 20 7.32-7.49(7H, m), 7.66(1H, dd, J=8.6Hz, 2.4Hz), 8.08(1H, d, J=2.4Hz), 8.17(1H, s).

IR (KBr, cm<sup>-1</sup>) : 3217, 3126, 3066, 3030, 2972, 2939, 2883, 1666, 1610.  
MS m/e : 414 (M<sup>+</sup>+1).

25 Example 56

4-Ethylcarbonyl-1-(4-hydroxyphenyl)-2-(2-methoxy-5-pyridinyl)-1H-imidazole

30 The target compound was obtained from 1-(4-benzylxyphenyl)-4-ethylcarbonyl-2-(2-methoxy-5-pyridinyl)-1H-imidazole obtained by Example 55 in the similar manner to that of Example 62 described later.

MP : 221-223°C.

1H NMR (DMSO-d<sub>6</sub>, δ) : 1.10(3H, t, J=7.3Hz), 2.95(2H, q, J=7.3Hz), 3.84(3H, s), 6.79-6.88(3H, m), 7.20(2H, dt, J=9.6 Hz, 2.7Hz), 7.66(1H, dd, J=8.7Hz, 2.4Hz), 8.07(1H, d, J=2.4Hz), 9.97(1H, s).

5 IR (KBr, cm<sup>-1</sup>) : 3215, 3136, 3053, 2978, 2947, 2900, 1676, 1603.

MS m/e : 324 (M<sup>+</sup>+1).

#### Example 57

10 1-(4-Benzylxyphenyl)-4-isopropylcarbonyl-2-(2-methoxy-5-pyridinyl)-1H-imidazole

The target compound (1.04g) was obtained from  
1-(4-benzylxyphenyl)-4-cyano-2-(2-methoxy-5-pyridinyl)-1H-imidazole obtained by Example 54-2 in the similar manner to that of Example 15 55.

MP : 118-120°C.

1H NMR (DMSO-d<sub>6</sub>, δ) : 1.14(6H, d, J=6.8Hz), 3.56-3.70(1H, m), 3.84(3H, s), 5.16(2H, s), 6.81(1H, d, J=8.5Hz), 7.13(2H, dd, J=9.1Hz, 2.3Hz), 7.32-7.49(7H, m), 7.67(1H, dd, J=8.5Hz, 2.4Hz), 8.08(1H, d, J=2.4Hz), 8.19(1H, s).

IR (KBr, cm<sup>-1</sup>) : 3126, 3064, 3033, 2968, 2875, 1660, 1608.

MS m/e : 428 (M<sup>+</sup>+1).

#### 25 Example 58

4-Isopropylcarbonyl-1-(4-hydroxyphenyl)-2-(2-methoxy-5-pyridinyl)-1H-imidazole

The target compound was obtained from 1-(4-benzylxyphenyl)-4-isopropylcarbonyl-2-(2-methoxy-5-pyridinyl)-1H-imidazole obtained by Example 57 in the similar manner to that of Example 62 described later.

MP : 185-187°C.

1H NMR (DMSO-d<sub>6</sub>, δ) : 1.14(6H, d, J=6.8Hz), 3.56-3.69(1H, m), 3.84(3H, s), 6.79-6.86(3H, m), 7.17-7.25(2H, m), 7.67(1H, dd, J=8.8Hz, 2.4Hz),

5 8.07(1H, d, J=2.4Hz), 8.14(1H, s), 9.98(1H, s).

IR (KBr, cm<sup>-1</sup>) : 3134, 2972, 2891, 2812, 2744, 2681, 2607, 1676, 1612.

MS m/e : 338 (M'+1).

Example 59

10 1-(4-Benzylxyphenyl)-4-cyclopentylcarbonyl-2-(2-methoxy-5-pyridinyl)-1H-imidazole

To a solution of 1-(4-benzylxyphenyl)-4-cyano-2-(2-methoxy-5-pyridinyl)-1H-imidazole obtained by Example 54-2 (0.8g) in tetrahydrofuran (8ml), 2N solution of cyclopentylmagnesium chloride in tetrahydrofuran (3.14ml) was added under stirring at 0°C.

After stirring at room temperature for 2hrs, the reaction mixture was poured into aqueous 10% potassium hydrogen sulfate and stirred at room temperature for 30min. The mixture was alkalized with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate, washed with water, dried over magnesium sulfate and evaporated in vacuo. The resulting precipitates were collected by filtration and washed with diisopropyl ether to give the target compound (0.82g).

25 1H NMR (200MHz, DMSO-d<sub>6</sub>, δ) : 1.57-1.949(m, 8H), 3.764(1H, t, J=7.9Hz), 3.84(3H, s), 5.156(2H, s), 6.81(1H, d, J=8.5Hz), 7.12(2H, d, J=9Hz), 7.328-7.501(7H, m), 7.669(1H, dd, J=8.5Hz, 2.5Hz), 8.078(1H, d, J=1Hz), 8.188(1H, s).

IR (KBr, cm<sup>-1</sup>) : 3122, 2947, 2868, 1658, 1608.

30 MS (ESI<sup>+</sup>, m/e) : 454 (M+H).

Example 60

**4-Cyclopentylcarbonyl-1-(4-hydroxyphenyl)-2-(2-methoxy-5-pyridinyl)-1H-imidazole**

The target compound was obtained from 1-(4-Benzylxyphenyl)-4-cyclopentylcarbonyl-2-(2-methoxy-5-pyridinyl)-1H-imidazole obtained by Example 59 in the similar manner to that of Example 62 described later.

1H NMR (200MHz, DMSO-d<sub>6</sub>, δ) : 1.577-1.968(8H, m), 3.761(1H, t, J=8Hz), 3.836(3H, s), 6.793-6.859(3H, m), 7.21(2H, d, J=7Hz), 7.667(1H, dd, J=9Hz, 2.5Hz), 8.069(1H, d, J=1.5Hz), 8.143(1H, s).  
IR (KBr, cm<sup>-1</sup>) : 3220, 3124, 2960, 1674, 1608.  
MS (ESI<sup>+</sup>, m/e) : 364 (M+H).

15      **Example 61**

**1-(4-Benzylxyphenyl)-2-(4-methoxyphenyl)-4-trifluoromethyl-1H-imidazole**

A mixture of N<sup>1</sup>-(4-Benzylxyphenyl)-4-methoxybenzamidine (1g), 3-bromo-1,1,1-trifluoropropanone (0.47ml) and sodium hydrogencarbonate (506mg) in isopropyl alcohol (10ml) was stirred at reflux condition overnight.

After cooling to room temperature, the reaction mixture was filtrated and evaporated in vacuo. Then the residue was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica-gel column chromatography eluting with (n-Hexane:Ethyl acetate=1:1) to give the target compound (0.55g) as an oil.

30      1H NMR (DMSO-d<sub>6</sub>, δ) : 3.75(3H, s), 5.16(2H, s), 6.86-6.92(2H, m), 7.09-7.13(2H, m), 7.25-7.50(9H, m), 8.08(1H, d, J=1.4Hz).  
IR (Neat, cm<sup>-1</sup>) : 3120, 3068, 2973, 2843, 1610.

MS m/e : 425 (M'+1).

**Example 62**

5       **1-(4-Hydroxyphenyl)-2-(4-methoxyphenyl)-4-trifluoromethyl-1H-imida  
zole**

10      **1-(4-Benzyloxyphenyl)-2-(4-methoxyphenyl)-4-trifluoromethyl  
-1H-imidazole obtained by Example 61 (0.55g) and dry 20% Pd(OH)<sub>2</sub>/C  
(200mg) in ethanol (10ml) and cyclohexene (5ml) was stirred at reflux  
condition for 2hrs and cooled to room temperature.**

After filtration, the reaction mixture was evaporated in vacuo  
to give the target compound (0.44g).

MP : 215-216°C.

15      **1H NMR (DMSO-d<sub>6</sub>, δ) : 3.74(3H, s), 6.81-6.92(4H, m), 7.16-7.30(4H,  
m), 8.03(1H, d, J=1.3Hz).**

**IR (KBr, cm<sup>-1</sup>) : 3149, 3103, 3037, 2964, 2910, 2829, 2690, 2611, 1649,  
1614.**

MS m/e : 335 (M'+1).

20

**[A] ANALGESIC ACTIVITY :**

**Effect on adjuvant arthritis in rats :**

**(i) Test Method :**

25      **Analgesic activity of a single dose of agents in arthritic rats  
was studied.**

Arthritis was induced by injection of 0.5 mg of *Mycobacterium*  
tuberculosis (Difco Laboratories, Detroit, Mich.) in 50μl of liquid  
paraffin into the right hind footpad of Lewis rats aged 7 weeks.  
Arthritic rats were randomized and grouped (n=10) for drug treatment  
30      based on pain threshold of left hind paws and body weight on day 22.

Drugs (Test compounds) were administered and the pain threshold  
was measured 2hrs after drug administration. The intensity of

hyperalgesia was assessed by the method of Randall - Selitto. The mechanical pain threshold of the left hind paw (uninjected hind paw) was determined by compressing the ankle joint with a balance pressure apparatus (Ugo Basile Co.Ltd., Varese, Italy). The threshold pressure of rats squeaking or struggling was expressed in grams. The threshold pressure of rats treated with drugs was compared with that of non-treated rats. A dose showing the ratio of 1.5 is considered to be the effective dose.

10 (ii) Test Results:

Test compound (Example No.)	Dose (mg/kg)	The coefficient of analgesic
3-2	3.2	>1.5
11	3.2	>1.5
24	3.2	>1.5
28	3.2	>1.5
40	3.2	>1.5
43	3.2	>1.5

[B] Inhibiting activity against COX-I and COX-II

(Whole Blood Assay):

(i) Test Method :

15 Whole blood assay for COX-I

Fresh blood was collected by syringe without anticoagulants from volunteers with consent. The subjects had no apparent inflammatory conditions and had not taken any medication for at least 7 days prior to blood collection.

20 500 $\mu$ l aliquots of human whole blood were immediately incubated with 2 $\mu$ l of either dimethyl sulfoxide vehicle or a test compound at final concentrations for 1hr at 37°C to allow the blood to clot. Appropriate treatments (no incubation) were used as blanks. At the end of the incubation, 5 $\mu$ l of 250mM Indomethacin was added to stop the reaction. The blood was centrifuged at 6000 x g for 5min at 4°C

to obtain serum. A 100 $\mu$ l aliquot of serum was mixed with 400 $\mu$ l methanol for protein precipitation. The supernatant was obtained by centrifuging at 6000 x g for 5min at 4°C and was assayed for TXB<sub>2</sub> using an enzyme immunoassay kit according to the manufacturer's procedure. 5 For a test compound, the results were expressed as percent inhibition of thromboxane B<sub>2</sub>(TXB<sub>2</sub>) production relative to control incubations containing dimethyl sulfoxide vehicle.

10 The data were analyzed by that a test compound at the indicated concentrations was changed log value and was applied simple linear regression. IC<sub>50</sub> value was calculated by least squares method.

#### Whole blood assay for COX-II

15 Fresh blood was collected in heparinized tubes by syringe from volunteers with consent. The subjects had no apparent inflammatory conditions and had not taken any medication for at least 7 days prior to blood collection.

20 500 $\mu$ l aliquots of human whole blood were incubated with either 2 $\mu$ l dimethyl sulfoxide vehicle or 2 $\mu$ l of a test compound at final concentrations for 15 min at 37°C. This was followed by incubation of the blood with 10 $\mu$ l of 5mg/ml lipopolysaccharide for 24hrs at 37°C for induction of COX-II. Appropriate PBS treatments (no LPS) were used as blanks. At the end of the incubation, the blood was centrifuged at 6000 x g for 5 min at 4 °C to obtain plasma. A 100 $\mu$ l aliquot of plasma was mixed with 400 $\mu$ l methanol for protein precipitation. The 25 supernatant was obtained by centrifuging at 6000 x g for 5min at 4°C and was assayed for prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) using a radioimmunoassay kit after conversion of PGE<sub>2</sub> to its methyl oximate derivative according to the manufacturer's procedure.

30 For a test compound, the results were expressed as percent inhibition of PGE<sub>2</sub> production relative to control incubations containing dimethyl sulfoxide vehicle. The data were analyzed by that a test compound at the indicated concentrations was changed log value and was applied simple

linear regression. IC<sub>50</sub> value was calculated by least squares method.

(ii) Test Results:

Test Compound (Example No.)	COX-I IC <sub>50</sub> ( $\mu$ M)	COX-II IC <sub>50</sub> ( $\mu$ M)
1-2	< 0.01	≥ 0.1
3-2	< 0.01	≥ 0.1
4-2	< 0.01	≥ 0.1
8	< 0.01	≥ 0.1
11	< 0.01	≥ 0.1
17	< 0.01	≥ 0.1
20	< 0.01	≥ 0.1
21	< 0.01	≥ 0.1
24	< 0.01	≥ 0.1
34	< 0.01	≥ 0.1
40	< 0.01	≥ 0.1
43	< 0.01	≥ 0.1

5 It appeared, from the above-mentioned Test Results, that the compound (I) or pharmaceutically acceptable salts thereof of the present invention have an inhibiting activity against COX, particularly a selective inhibiting activity against COX-I.

10 Additionally, it was further confirmed that the compounds (I) of the present invention lack undesired side-effects of non-selective NSAIDs, such as gastrointestinal disorders, bleeding, renal toxicity, cardiovascular affection, etc. So compound (I) or a salt thereof is expected to be useful as medicament.

15 The object compound (I) or pharmaceutically acceptable salts thereof of this invention possesses COX inhibiting activity and possesses strong anti-inflammatory, antipyretic, analgesic, antithrombotic, anti-cancer activities, and so on.

20 The object compound (I) and pharmaceutically acceptable salt thereof, therefore, are useful for treating and/or preventing COX mediated diseases, inflammatory conditions, various pains, collagen

diseases, autoimmune diseases, various immunological diseases, thrombosis, cancer and neurodegenerative diseases in human beings or animals by using administered systemically or topically.

More particularly, the object compound (I) and pharmaceutically acceptable salts thereof are useful for treating and/or preventing inflammation and acute or chronic pain in joint and muscle [e.g. rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, juvenile arthritis, etc.], inflammatory skin condition [e.g. sunburn, burns, eczema, dermatitis, etc.], inflammatory eye condition [e.g. conjunctivitis, etc.], lung disorder in which inflammation is involved [e.g. asthma, bronchitis, pigeon fancier's disease, farmer's lung, etc.], condition of the gastrointestinal tract associated with inflammation [e.g. aphthous ulcer, Crohn's disease, atopic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, etc.], gingivitis, inflammation, pain and tumescence after operation or injury, pyrexia, pain and other conditions associated with inflammation, particularly those in which lipoxygenase and cyclooxygenase products are a factor, systemic lupus erythematosus, scleroderma, polymyositis, tendinitis, bursitis, periarteritis nodose, rheumatic fever, Sjogren's syndrome, Behcet disease, thyroiditis, type I diabetes, nephrotic syndrome, aplastic anemia, myasthenia gravis, uveitis contact dermatitis, psoriasis, Kawasaki disease, sarcoidosis, Hodgkin's disease, Alzheimers disease, or the like.

Additionally, the object compound (I) or a salt thereof is expected to be useful as therapeutical and/or preventive agents for cardiovascular or cerebrovascular diseases, the diseases caused by hyperglycemia and hyperlipemia.

And compound (I) or a salt thereof is expected to be useful as analgesic agent, which is usable for treating or preventing pains caused by or associated with acute or chronic inflammations, for example rheumatoid arthritis, osteoarthritis, lumbar rheumatism, rheumatoid

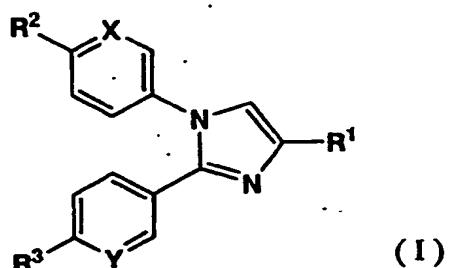
spondylitis, gouty arthritis, juvenile arthritis; lumbago; cervico-omo-brachial syndrome; scapulohumeral periarthritis; pain and tumescence after operation or injury.

5        Although the present invention has been fully described by way of example, it is to be understood that various changes and modifications will be apparent to those skilled in the art. Therefore, unless otherwise such changes and modifications depart from the scope of the present invention hereinafter defined, they should be construed as being  
10      included therein.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of the formula (I):



5

[wherein

R¹ is (lower)alkyl, halogen-substituted (lower)alkyl,

hydroxy-substituted (lower)alkyl, cycloalkyl, carbamoyl,

10

N-[(lower)alkyl]carbamoyl, N,N-di[(lower)alkyl]carbamoyl,

formyl, (lower)alkanoyl, carboxy, [(lower)alkoxy]carbonyl,

cyano, cycloalkylcarbonyl or heterocycliccarbonyl;

R² is halogen, cyano, hydroxy, (lower)alkoxy,

aryl[(lower)alkyl]oxy, [(lower)alkoxy]carbonyl,

15

carbamoyl, formyloxy, (lower)alkanoyloxy,

[(lower)alkyl]sulfonyloxy, [halogen-substituted

(lower)alkyl]sulfonyloxy or carboxy;

R³ is (lower)alkoxy, hydroxy, amino, [(lower)alkyl]amino, or  
di[(lower)alkyl]amino;

20

X and Y are each CH or N]

or pharmaceutically acceptable salts thereof.

2. A compound according to Claim 1.

wherein

25 R¹ is (lower)alkyl, halogen-substituted (lower)alkyl, cycloalkyl,  
N,N-di[(lower)alkyl]carbamoyl, (lower)alkanoyl, or cyano;

R² is halogen, cyano, hydroxy, or lower alkoxy;

R³ is lower alkoxy;

X and Y are each CH, X is N and Y is CH, or X is CH and Y is N;  
or pharmaceutically acceptable salts thereof.

3. A medicament comprising a compound of Claim 1 or 2 as an active  
5 ingredient.

4. A pharmaceutical composition comprising a compound of Claim 1 or  
2 as an active ingredient, in association with a pharmaceutically  
acceptable carrier or excipient.

10 5. A method for treatment and/or prevention of inflammatory conditions,  
various pains, collagen diseases, autoimmune diseases, various immunity  
diseases, thrombosis, cancer or neurodegenerative diseases which  
comprises administering an effective amount of the compound of Claim  
15 1 or 2 to human beings or animals.

6. The compound of Claim 1 or 2 for use in the treatment and/or prevention  
of inflammatory conditions, various pains, collagen diseases,  
autoimmune diseases, various immunity diseases, thrombosis, cancer or  
neurodegenerative diseases in human beings or animals.  
20

7. Use of the compound of Claim 1 or 2 for the manufacture of a medicament  
for treatment and/or prevention of inflammatory conditions, various  
pains, collagen diseases, autoimmune diseases, various immunity  
25 diseases, thrombosis, cancer or neurodegenerative diseases in human beings  
or animals.

8. The analgesic agent comprising the compound of Claim 1 or 2, which  
is usable for treating and/or preventing pains caused by or associated  
30 with acute or chronic inflammations.

9. The analgesic agent of Claim 8, which is usable for treating or

5 preventing pains caused by or associated with rheumatoid arthritis, osteoarthritis, lumbar rheumatism, rheumatoid spondylitis, gouty arthritis, juvenile arthritis; lumbago; cervico-omo-brachial syndrome; scapulohumeral periarthritis; pain and tumescence after operation or injury.

10. A commercial package comprising the pharmaceutical composition containing the compound (I) identified in Claim 1 or 2 and a written matter associated therewith, wherein the written matter states that  
10 the compound (I) can or should be used for preventing or treating inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, cancer or neurodegenerative diseases.

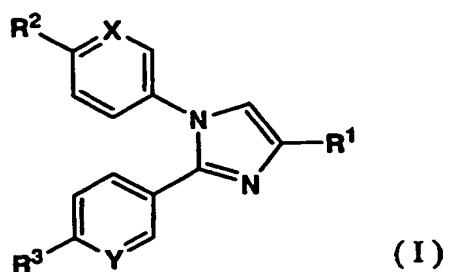
DATED this 1<sup>st</sup> day of August, 2003

Fujisawa Pharmaceutical Co., Ltd.

By DAVIES COLLISON CAVE  
Patent Attorneys for the Applicant

A B S T R A C T

A compound of the formula (I):



5

wherein

R¹ is cyano, etc;

R² is hydroxy, etc;:

10 R³ is (lower)alkoxy, etc;:

X and Y are each CH or N;

or pharmaceutically acceptable salts thereof, which are useful as a medicament.

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